SURGERY
GYNECOLOGY AND OBSTETRICS
An International Magazine, Published Monthly

VOLUME 74 JANUARY, 1942 NUMBER 1

ERYTHROBLASTOSIS NEONATORUM

An Obstetrical-Pathological Study of 47 Cases

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ERYTHROBLASTOSIS neonatorum, or fetalis, has become a term used in the current literature when referring to hydrops fetalis, icterus gravis, and congenital anemia of the newborn, although Appleberg-Ulfsparre, Arnold and Downey, prefer the original terminology. These diseases of the fetus have in common a varying degree of erythroblastemia and erythroblastosis which is most marked in the hydrops variety. When immature white cells are numerous, the term erythroleucoblastosis is sometimes used, and in the earlier reports of both Jakesch and Klebs in 1878, and of Sanger in 1888, the condition was called fetal leucemia.

Hydrops fetalis has been recognized for centuries according to Ballantyne, who in 1898 collected 70 cases from the literature since 1614. The hematological picture was added by Schridde in 1910, and Rautman named the disease erythroblastosis in 1912. Icterus of the newborn has also been observed for centuries, but it remained for Blomfield in 1901 to differentiate physiological jaundice from icterus gravis. Even as late as 1908 Pfannenstiel held that icterus gravis was an intensification of physiological jaundice. The familial nature of icterus gravis was noted by Buchan and Comrie, and they also called attention to the large numbers of nucleated red cells in the circulating blood as well as to the hematopoiesis in the liver and spleen. Ultimately, icterus gravis was included in the syndrome of erythroblastosis, and the subsequent reports of von Gierke, Yllpo, de Lange and Arntzenius, and others have substantiated this relationship. Although anemia is seen secondary to or associated with hydrops and icterus, congenital anemia *per se* was correlated with erythroblastosis neonatorum by Ecklin in 1919, with confirmatory reports by Susstrunk, Abt, and others. However, Hellman and Hertig regard the anemia only as a secondary manifestation of icterus gravis; to this we take exception, because of our own experience with 3 cases, as well as the reports in the literature. The occurrence of anemia and hydrops in infants of the same family as reported by Passachoff and Wilson, and anemia and icterus as reported by Diamond, Blackfan and Baty, may be regarded as further evidence that anemia is a separate entity.

It is often difficult to classify a given case of erythroblastosis fetalis into the hydropic, icteric, or anemic types because of the overlapping of symptoms. However, the prominent clinical feature is selected when designating

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erythroblastosis as to type. During the course of this study, we have observed 3 cases which had hemorrhagic diathesis as the first outstanding clinical sign. Such association is illustrated by Case 3. There were 3 other infants in our study that had erythroblastosis and erythroblastemia without clinical hydrops, icterus, anemia, or hemorrhagic diathesis. They probably died before any of these complications had time to develop, since 2 died before delivery. Two of these cases were proved by autopsy, while the third was too badly macerated for histological interpretation, but the cord blood was sufficiently well preserved to give the diagnosis. References were also obtained in the literature to reports of erythroblastosis without hydrops, icterus, or anemia by Salomonsen, de Lange and Ferguson.

A classification of erythroblastosis neonatorum based on our experience with 47 cases and substantiated by reports in the literature, is presented: erythroblastosis with hydrops, 16 cases; erythroblastosis with icterus, 22 cases; erythroblastosis with anemia, 3 cases; erythroblastosis with hemorrhagic diathesis, 3 cases; erythroblastosis without hydrops, icterus, anemia, or hemorrhagic diathesis (*unclassified*), 3 cases.[1]

Such a classification has academic value in clarifying our knowledge of the disease. It also has practical value since the infant mortality rate varies with the different types of the disease, as will be shown subsequently.

INCIDENCE

The incidence of erythroblastosis varies according to the type of the disease. The hydrops infants have an incidence of 1:1348 in our material, and 1:3800 in the series of Wolfe and Neigus. The icterus form in our series was 1:876 as compared to 1:1500 found by Hellman and Hertig. This wide range is presumably due to a failure to recognize and diagnose the cases as has been our experience. In the years 1933 to 1935, we observed only 7 cases in 10,819 premature and full term deliveries, or 1:1545. During the period 1936 to 1940, we have had 40 cases in 17,520 deliveries, or 1:438; an increase of nearly 400 per cent during the period of the present study!

Erythroblastosis is not frequently encountered, yet one must be acquainted with it for definite reasons. The incidence is 100 per cent for the mother that bears one of these infants, particularly when the baby dies, as so many of them do. Erythroblastosis is responsible for 3.2 per cent of our fetal deaths. The doctor-patient relationship may become strained if an infant with erythroblastosis is delivered by cesarean section, as in cases reported by A. F. Abt (Smyth's case), Bonney and Morton, and Pallos. A knowledge of this disease is necessary in making a differential diagnosis of other diseases of the newborn. It is noted that the medical examiners of the New York State Board asked a question on erythroblastosis in the examination on obstetrics in 1938. Finally, a research physician need feel no chagrin if his efforts bring knowledge and understanding of a disease, even though much cannot be done from the standpoint of prevention and treatment. Prophylactic antepartum therapy for the child, for which Ballantyne first raised a plea, may be shown to have a practical application in erythroblastosis as it has in syphilis, and to that end, this study is dedicated.

MATERNAL DATA

Most of the following data have been obtained from 16 mothers bearing infants with hydrops, and 22 with icterus gravis. Inclusion of anemic, hemorrhagic, and unclassified types would be somewhat controversial, and their number is too small anyway to be statistically important, so they have not been tabulated except when stated.

Age. The average maternal age was 31.3 and 30.0 years, for the hydrops and icterus groups, respectively. Hellman and Hertig have recorded similar ages for the two groups.

Race. It is generally believed that erythroblastosis is seen more frequently in patients having Mediterranean ancestry, while Otto reports a high incidence in the Scandinavian race. In our material, nearly all of the races attending a clinic were represented. However, in proportion to the clinic population, 30 per cent were Irish, in contrast to 14.5 per cent for the clinic; and 11 per cent were negroes, versus 6.6 per cent for the clinic, showing a higher incidence in the Irish and negro race.

Parity. In the total group of 47 mothers, there were only 3 primiparas, making multiparity a decided factor in 92 per cent of the patients. Potter reports 38 cases all in multiparas, and many authors state that the first-born escapes the disease. Schumann found 5 primiparas in 30 mothers that de-

[1] A 4th case of the *unclassified* type of erythroblastosis has been observed recently, born to a mother who had 3 previous infants with icterus gravis.

livered infants with universal edema. The average parity was 3.2 and 3.1 for the two groups in contrast to 5.2 and 3 in the series of Hellman and Hertig.

Duration of gestation. The average was 36.3 weeks for the hydrops group and 39 weeks for the icterus group, showing that the former were born 1 month or more prematurely. In Capon's series of hydrops cases, the average duration was 33 weeks.

Complications of pregnancy. Capon, Hellman and Hertig, Darrow, and others state that the mother shows no characteristic pathognomonic signs. This may be true, but developments do occur during pregnancy and labor that should arouse suspicion, especially in the hydrops form of erythroblastosis, and include: excessive uterine enlargement ("hydramnios") in 50 per cent, and toxemia of pregnancy in 31 per cent of the hydrops cases. Premature separation of the placenta, jaundice, and diabetes were present in several mothers.

Uterine enlargement out of proportion to the duration of pregnancy was frequently diagnosed as "hydramnios" clinically, and it has been so designated in the literature. The excessive uterine enlargement was found to be due to the combined weight of the placenta and infant, which in the hydrops cases averaged 4,674 grams, or 10.2 pounds. This is considerable for an average period of gestation of only 36 weeks. Figure 1 shows the placenta and infant of Case 1 which together weighed 4,950 grams, 10.7 pounds; the period of gestation was only 33 weeks. The edema of the infants makes them weigh more, so that they may be regarded as mature on the basis of weight when actually they are premature.

The incidence of toxemia of pregnancy was increased in both types of erythroblastosis, but was highest in the hydrops cases. Schumann found that 62 per cent of the cases reviewed by him had albuminuria and edema. Others, including de Lange, and Hellman and Hertig, found a high incidence of toxemia. Williamson and Vecchi have each reported a case of hydrops associated with postpartum eclampsia, and because of the rarity of such reports we record our own at this time.

CASE 1. Mrs. S. H., aged 27 years, Irish, parity 2–0–1–1,[1] who was delivered 3 years previously of an infant which died of icterus gravis. The Wassermann reaction was negative. The present pregnancy was complicated by an excessive weight gain of 25 kilograms, 55 pounds, by the thirty-second week of gestation. At this time an oliguria developed with

[1] The patient has had 2 full term, 0 premature deliveries, 1 abortion, and has 1 living child. Same explanation holds for Cases 3–6.

Fig. 1. Case 1. Macerated fetus with hydrops type of erythroblastosis, weight, 2,750 grams at 33 weeks' gestation; weight of placenta, 2,200 grams. From Stander, H. J. *Williams Obstetrics*, 8th ed., 1941.

3 plus albumin in the urine, the blood pressure rising to 165/110 and remaining at that level. She received the routine treatment for pre-eclampsia, including intravenous glucose. The nonprotein nitrogen rose from 29.2 milligrams per 100 cubic centimeters to 50.8, the uric acid from 5.6 milligrams to 7.6 milligrams; the carbon dioxide combining power decreased from 32.9 to 27.7 volumes per cent. Polyhydramnios was suspected clinically because of the excessive uterine enlargement. Roentgenographic studies were, therefore, conducted in order to determine the presence of soft tissue edema or abnormality of the fetus, since erythroblastosis was suspected. No halo or corona was seen about the fetal head, but, within the uterus, the infant had a Buddha-like habitus caused by the enlarged abdomen (Fig. 10b).

An induction of labor using castor oil, quinine, and an enema was successful, and, during the first stage of labor, the fetal heart was lost. The patient was delivered by breech extraction after a 7 hour labor. There was a postpartum hemorrhage of 700 cubic centimeters, which was attributed in part to the large placenta weighing 2,200 grams. It and the infant, which weighed 2,750 grams, had a combined weight of 4,950 grams, 10.2 pounds. Both are shown in Figure 1. The infant should have weighed about 1,600 grams for this period of gestation. Because of the postpartum hemorrhage, a blood transfusion was given to the mother. Three hours after delivery the mother developed two convulsive seizures. At this time she was given oxygen and molar lactate solution. Sixteen hours later, the nonprotein nitrogen had risen to 85.4 and the uric acid on the third postpartum day was 12.3 milligrams. Kidney function tests postpartum revealed a urea clearance of 73.5 per cent in 2 hours.

The first maternal prothrombin determination was done immediately postpartum. It was 68 per cent of normal, and on the following day it was 61 per cent. Thyloquinone was given (2 mgm.) intramuscularly, and on the third postpartum day the prothrombin was still 61 per cent, indicating probable failure of the liver to utilize the thyloquinone because of damage. This patient has been followed at intervals in the past 10 months and the prothrombin level is still considerably lower than normal. Further evidence of liver damage may be obtained from a study of the serum proteins during pregnancy, for levels as low as 3.4 grams per 100 cubic centimeters were found.

Examination of the cord blood revealed 458 normoblasts and 87 erythroblasts per 100 white cells. The total white count was 50,000 of which 20,700 were nucleated red cells. The mean red cell diameter was 10.2 μ. There were many immature white cells in the smear. The hemoglobin was 12 per cent (2 gm., Sahli); red blood corpuscles, 500,000; color index, 1.2; volume index, 1.5 The prothrombin and fibrinogen concentration of the cord blood were too low for determination—fetal death several hours previous. The serum proteins were also very low, 1.9 grams per 100 cubic centimeters.

Autopsy revealed the characteristic pathology of the hydrops type of erythroblastosis. The liver was examined with interest because of the hydrops as well as the toxemia in the mother, and it showed marked degeneration of the liver cords with associated postmortem changes.

Amniotic fluid. The color of the amniotic fluid has been described by many authors and the consensus is that is usually has a golden yellow color. In some of our cases, the color was often obscured by the passage of meconium resulting from fetal distress, which is frequently seen in erythroblastosis. A golden yellow amniotic fluid observed when the membranes rupture prematurely should arouse suspicion (See Case 6.)

Fetal distress within the uterus. Auscultation of the fetal heart often revealed fetal distress which is indicative of intrauterine asphyxia. Sometimes the fetal heart was lost before the onset of or during labor. All the hydrops infants born alive and 50 per cent of the icterus infants required resuscitation by means of carbon-dioxide-oxygen mixture or the use of the Flagg apparatus. The fetal distress and systolic bruit were often helpful signs in making a correct antepartum diagnosis. The former also provided the indication for a large number of operative deliveries.

Operative incidence. In the hydrops group, the operative incidence was 50 per cent, and it was 23 per cent in the icterus group (clinic 10 per cent).Two mothers were delivered by cesarean section; 1 was performed for premature separation of the placenta and the other because of 3 previous sections. Chief indication for operative interference (forceps) was fetal distress which occurred in 56 per cent.

Blood loss in the third stage of labor. The average blood loss in the hydrops group was 461 cubic centimeters which is greater than the average of 271 cubic centimeters for the clinic; while the amount in the icterus group was not increased, namely 213 cubic centimeters. The increase in the hydrops group was caused by postpartum hemorrhage which occurred in 5 cases, or 31 per cent, whereas only 1 case with icterus had a hemorrhage. The excessive bleeding in the hydrops group was caused by atony due to the overdistended uterus, large size of the placenta with an increased uterine surface to bleed, friability of the cotyledons with retained portions requiring manual removal as in one case, and the factors associated with operative delivery.

Placenta. The average weight in the hydrops group was 1,254 grams; the largest weighed 2,200 grams (Fig. 1). The average weight of the infants was 3,420 grams, giving an infant-placenta ratio of 3:1—normal 6:1. The average weight in the icterus cases was 692 grams; the largest weighed 1,000 grams. The average weight of the infants in this group was 3,442 grams so that the normal ratio of 6:1 was obtained.

Inspection of the placentas of the infants with hydrops invariably revealed a pale maternal surface, deeply fissured, forming cotyledons which were friable. The fetal surface and membranes were stained yellow in 6 of our cases; in others, it was gray and glistening. On standing, the placenta basin filled rapidly with a yellow colored serum, so that in a short time the placenta lost as much as 500 grams in weight. The large size of the placenta is thought to be a response on the part of the fetal organism to faulty metabolism requiring an increase in the placental surface. The placenta of the icterus infants was of normal size as a rule, there was little or no edema, the maternal surface had a normal red color, with normal cotyledons; the fetal membranes were discolored in 4 cases.

Previous to the present study begun in 1936, only 1 placenta had been saved for examination, which has been the experience of most writers. However, in the past 5 years we have examined 26 placentas, which will be reported elsewhere in greater detail. Suffice it to state for the present that the placentas of the hydrops cases bear a close resemblance to syphilis so that an erroneous diagnosis may be made. There is abnormal basophilia; the villi are large and edematous with signs of immaturity, as indicated by focal persistance of the Langhans layer and the presence of Hof-

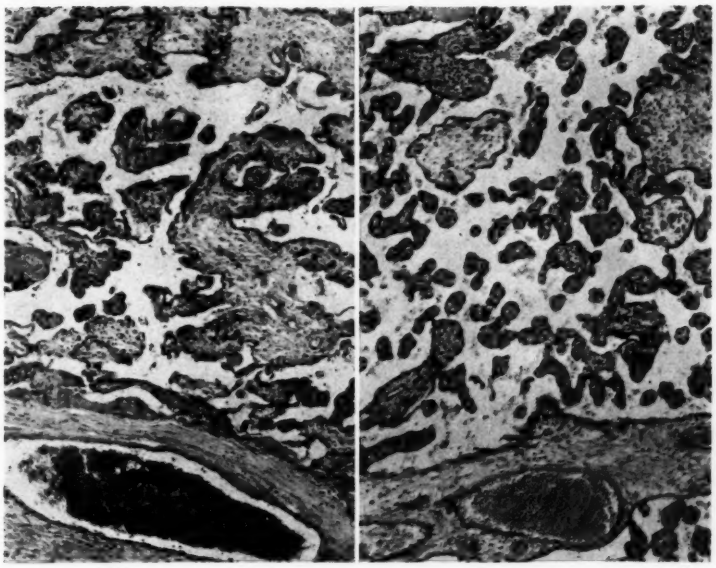

Fig. 2. Photomicrographs of placentas in erythroblastosis. Low power. a, left, Hydrops case. Note large, edematous, immature villi and fetal vessel filled with nucleated erythrocytes. b, Icterus case. Villi are more mature although some have edema. Fetal vessel has fewer nucleated red cells.

bauer cells (Fig. 2a). The amnion and chorion often exhibit cells laden with a brownish pigment similar to that seen in the fetal liver and other organs. The first histological report of the placenta was made by Goormaghtigh in 1927. He observed foci of hematopoiesis as have Hellman and Hertig. We regard the immature red cells, erythroblasts and normoblasts in the fetal vessels of the placenta as of greater diagnostic value.

The placentas of the icteric infants showed more mature villi although some showed slight edema. The fetal vessels contained fewer normoblasts and occasional erythroblasts. Basophilia was also less marked (Fig. 2b).

Familial history. This term is a misnomer. A better designation would be "obstetrical history," or "maternal history," since the mother gives a history of bearing infants with the disease. Her family history as well as that of the husband fails to reveal a similar tendency. Erythroblastosis in repeated pregnancies has been reported by de Lange and many others.

Erythroblastosis usually appears in the second or third, or even the fifth pregnancy, as a rule, although primiparas may have infants with the disease. When the first born has had erythroblastosis, it is very likely to recur in subsequent infants. In the literature, Buhrman and Sanford, Commandeur, Diamond et al., Fleishmann and Wolff, Jatho, Zimmermann and Yannett, each report erythroblastosis in the first pregnancy with repetition in successive pregnancies. Their cases together with 3 of our own have had a total of 27 pregnancies resulting in only 1 healthy infant without erythroblastosis.

The occurrence of erythroblastosis in terms of total number of pregnancies was 34.2 per cent for the hydrops group, and 31.4 per cent in the icterus group. These percentages are in close agreement with those of Macklin, 30 and 58 per cent, respectively. The hydrops group had more abortions than the icterus group, as well as history of erythroblastosis in previous infants. These mothers have no difficulty in becoming pregnant, which speaks for the normalcy of the ova and sperm.

There were 131 pregnancies in the hydrops and icterus groups resulting in 43 infants with erythroblastosis. These were studied as to the appearance of erythroblastosis, and it was found that the lowest incidence occurred in the first pregnancy and that the tendency increased with successive pregnancies. The percentages were approximately the same for both the hydrops and icterus groups. Recurrence of erythroblastosis after its first appearance is about 50 per cent for the hydrops group and 40 per cent

Fig. 3. Infants with hydrops type of erythroblastosis. a, left, Case 5. Child weighed 3,070 grams at 37 weeks' gestation; placenta weighed 2,100 grams. Pronounced asphyxia; fluid was aspirated from chest and abdomen as an aid to resuscitation. Death occurred 15 minutes after delivery. b, Dissection to show enlarged heart, liver, and spleen. (From Wolfe, S. A., and Neigus, I. *Am. J. Obst.*)

for the icterus group. Hellman and Hertig report 50 and 80 per cent for the two groups, respectively.

The delivery of normal infants after the appearance of erythroblastosis in the previous infant was observed in 4 patients (not primiparas). These infants had no special prenatal therapy, nor was there a change in husbands. However, these mothers had had normal infants prior to the appearance of erythroblastosis.

Multiple pregnancy. Erythroblastosis has been reported in twins by Wooley, Oberndorfer, MacMahon, Abt, Buhrman and Sanford, and Andrews and Miller. Veterinarians have observed the hydrops form in one of a litter of pups. Sometimes one twin is normal, as in de Lange's case. Macklin found in her survey of the literature that when one twin had hydrops, the other was normal in 8 out of 9 cases; whereas with icterus, both twins were so afflicted in 5 out of 7 cases. Unfortunately, most of the reports fail to distinguish between identical or fraternal twins. This is of importance since erythroblastosis may be a congenital disturbance affecting only one twin as in MacMahon's case of identical twins, whereas both of the monochorionic twins reported by Snyder and Ford had fetal hydrops.

Of our 47 cases, only one mother had single ovum twins (female), one of which was deadborn and macerated and had the unclassified type of erythroblastosis; the other died at the age of 2 days of congenital anemia, prematurity, and cardiac hypertrophy. Other features of this case are as follows:

Case 2. Mrs. E. T., Hungarian, 26 years old, primigravida, who had an uneventful pregnancy, the diagnosis of twins having been confirmed by x-ray. The Wassermann was negative. Labor began spontaneously in the thirty-eighth week of gestation, and after a 9 hour labor twin A, weighing 2,150 grams, was delivered by breech extraction. It lived for 2 days and developed petechiae and convulsions. Examination of the cord blood at birth revealed a red corpuscle count of 3,500,000; hemoglobin 12.5 grams; the white cell count, 55,000, and 20 erythroblasts and 95 normoblasts per 100 white cells. The cord prothrombin was 7 per cent of normal; the fibrinogen was 0.25 grams per cent, without evidence of hemorrhagic diathesis. During life, two transfusions were given and 2 milligrams of synthetic vitamin K (thyloquinone, Squibb). The infant died on the second day of life. The prime pathological features comprised large heart weighing 39 grams, hematopoiesis of the liver and spleen, with areas of focal necrosis in the former.

Twin B was a deadborn and macerated female weighing 2,050 grams. A smear of cord blood showed 6 erythroblasts and 72 normoblasts per 100 white cells. The white cell count was 31,000. Since the blood was hemolyzed, no further studies were made. Autopsy revealed marked autolysis so that histological diagnosis could not be carried out. The placenta weighed 890 grams, and examination of the membranes confirmed the diagnosis of single ovum twins. Grossly, the placenta revealed deeply stained membranes for twin B, and histologically the outstanding criteria were the normoblasts in the fetal vessels.

The diagnosis of erythroblastosis of the *unclassified* type was made on twin B, while twin A was considered as having the anemic form of the disease. It is probable that had twin B been born alive, it might have developed anemia or icterus and could then have been classified in the conventional manner.

Blood studies. Fifteen mothers (7 hydrops) had a complete hematological examination including a smear, while the rest had an average of two or more hemoglobin determinations during the antepartum course. All were within normal limits, save for a mild anemia in 2 cases. Moore and Pastore have reported a case of erythroblastic splenomegaly in a mother who delivered a normal infant. Doi reports the occurrence of erythroblastosis in the blood of

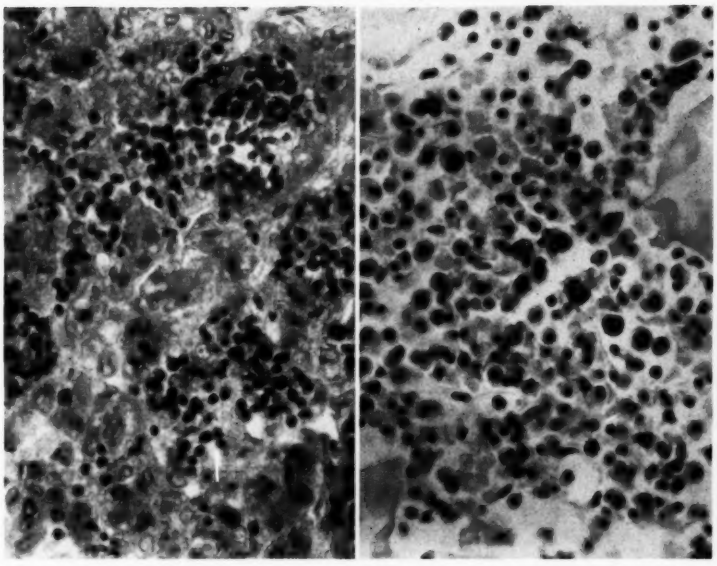

Fig. 7. Photomicrographs of liver and bone marrow in hydrops type of erythroblastosis. ×190. a, left, Liver, showing hematopoietic foci and cellular degeneration. b, Bone marrow showing marked hyperplasia of granular elements, numerous immature erythrocytes.

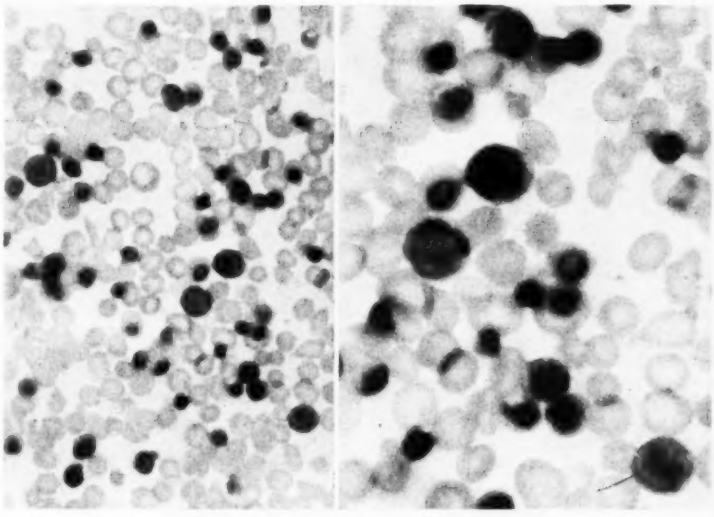

Fig. 8. Photomicrographs of cord blood. Low and high magnification. Note large erythroblasts and smaller normoblasts. (See Fig. 9, frontispiece.)

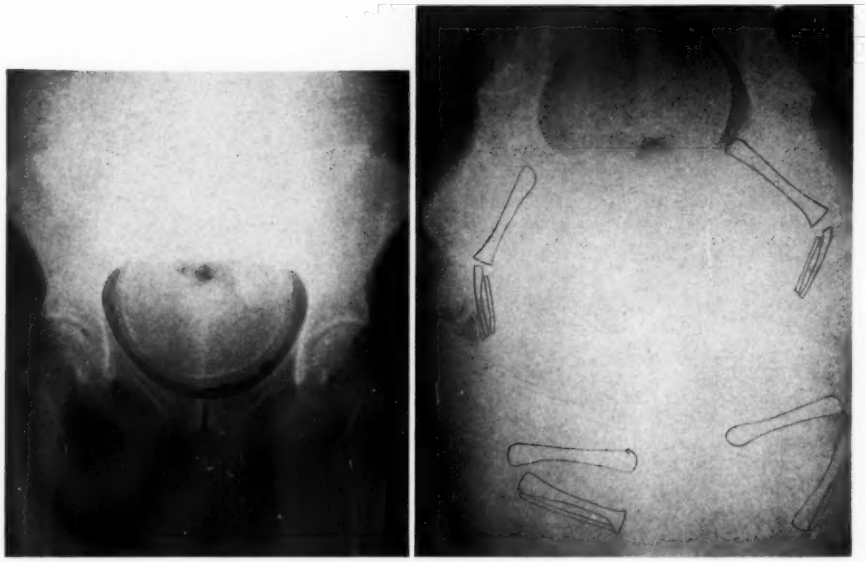

Fig. 10. Roentgenograms showing hydrops fetalis *in utero*. (Retouched.) a, left, Fetal head has "halo" due to edema of scalp. b, Habitus of fetus conforms to a Buddha, or frog-like posture due to abdominal enlargement caused by ascites and a large liver.

mothers with "pregnancy kidney" and eclampsia. The Kline or Wassermann reaction was negative in all of the 47 cases. There was not the slightest indication of syphilis, which is of significance since the placenta was occasionally so diagnosed. The Rh[1] agglutinin of Levine and Katzin was absent in several mothers.

The blood chemical constituents were studied in 9 mothers with the following average results per 100 cubic centimeters of blood:

	Mothers with erythroblastosis	Control at term (Stander)
Nonprotein nitrogen	31.2 mgm.	28.0 mgm.
Urea-nitrogen	13.7 mgm.	12.5 mgm.
Uric acid	5.1 mgm.	3.0 mgm.
Chlorides	515.0 mgm.	494.0 mgm.
Sugar	83.0 mgm.	80.0 mgm.
Carbon dioxide combining power	38.1 vol. %	48.0 vol. %
Icterus index	5–9 units	2–3 units

The chief deviation from normal was seen in the blood uric acid and carbon dioxide combining power which was explained on the presence of toxemia in most of the mothers studied. The icterus index was also elevated, and ranged from 3 to 20 units in 7 mothers with hydrops, and averaged 5 units in 3 mothers having infants with icterus gravis (normal 2 to 3 units). The icterus index of the cord blood of the infants was 91 units and 66 units for the two types, respectively (normal 10 to 15 units). Two mothers had clinical jaundice, and Buhrman and Sanford observed it in one of their cases in the last month of pregnancy. It is due either to a diffusion of bilirubin from the infant through the placenta into the maternal circulation, or to the maternal liver dysfunction, or both of these factors.

The serum proteins were studied in 3 mothers and the average of 21 determinations was 5.0 grams per 100 cubic centimeters, which is below the normal for a pregnant patient at term. Case 1 had as little as 3.4 grams, and she delivered an infant with hydrops that had 1.9 grams per 100 cubic centimeters. Prothrombin determinations, in which the technique of Warner, Brinkhous, and Smith were used, showed varying concentrations ranging from 20 to 100 per cent.

Mortality. All of the 47 mothers survived.

[1]Rh is an antigen present in the red cells of all Macacus rhesus monkeys (hence the name), and in 85 per cent of human blood, while 15 per cent of the population at large is Rh negative. According to Levine (personal communication), 90 per cent of the mothers having infants with erythroblastosis are Rh negative. The blood of the fathers and the infants is usually Rh positive.

INFANTS' DATA

These are presented for the most part on the basis of 16 cases of the hydrops and 22 cases of the icterus gravis types of erythroblastosis.

Sex. In the hydrops group, there were 9 males and 7 females, whereas in the icterus group there was a preponderance of males, 14 to 8.

Birth weight. The average weight of the hydrops group was 3,420 grams, which is 1,000 grams more than for the average of 36 weeks' gestation. The

average weight in the icterus group was 3,442 grams, which agrees with the duration of 39 weeks' gestation. There was 1 premature child in this group.

Appearance at birth. The hydropic child has marked pitting edema, the neck is short, and there is a suggestion of Mongoloid facies. The abdominal and thoracic distention is due to effusion and a large liver, and may be so marked that the natural posture of the child is prevented, causing it to assume a Buddha-like position, as was sometimes observed *intra uterum* by x-ray (Fig. 10b). The arms and legs seem shorter than normal and the skin is usually macerated if the child is stillborn, as many of them are (Figs. 1 and 3a). The vernix may have a yellow color. The child with the icterus form of erythroblastosis is usually born alive and may or may not be slightly yellow at birth, or become so soon thereafter (Fig. 4, frontispiece). The child may require resuscitation. Liver and spleen are usually enlarged.

Congenital anomalies. Such defects were found in 10 of the 47 infants, or 21 per cent, and included harelip and cleft palate, spina bifida, hydrocele, supernumerary fingers, cervical rib, urethral stricture, and an interventricular septal defect. Murphy gives the incidence of congenital defects in deceased liveborn and stillborn infants as 0.54 and 0.68 per cent, respectively, so that the incidence in our infants with erythroblastosis is approximately 40 times greater. Weber and Scholtz have described a case of hydrops fetalis that had multiple congenital anomalies; Vecchi's case had polydactylia and cystic kidneys, and the case reported by Bourret and Lathoud also had cystic kidneys. Murphy found that families possessing two or more malformations had subsequent offspring with the same deformity in 50 per cent of the infants. This corresponds closely to our incidence of 50 and 40 per cent for the hydrops and icterus cases, respectively, and to the 50 per cent incidence reported by Macklin. It seems from this evidence that any theory must consider the congenital aspect when used to explain the pathogenesis of erythroblastosis; enzygotic twins sometimes have the disease, which is further evidence of its congenital nature.

Symptoms in addition to hydrops and icterus. The clinical differentiation of erythroblastosis into hydrops, icterus, anemia, and hemorrhagic forms may be difficult because of an overlapping of signs. For instance, a baby with hydrops may develop jaundice (Case 4), and an icteric infant may develop focal edema about the eyelids and scrotum, while both of these types may also have an associated anemia. They may also show evidence of hemorrhagic diathesis as a coexisting complication, or it may be the first evidence *per se* of erythroblastosis, as in Case 3. Finally, a few infants may die *in utero* (Case 2), or may not live long enough to develop any of the usual signs of hydrops, icterus, or anemia. Nevertheless, they may have erythroblastosis as we have observed in 4 cases, and these have been placed in an *unclassified* group, and have already been referred to.

Of the 25 infants born alive and having erythroblastosis, the following clinical signs were observed: focal edema in 16 cases; pallor in 12; skin petechiae in 16; visceral hemorrhages in 7, 3 of which were thought to be hemorrhagic disease until blood studies showed the erythroblastosis; cyanosis in 17; dyspnea in 10; convulsions in 4. Many infants had two or more of these signs in addition to the hydrops or icterus. The high incidence of hemorrhagic diathesis, 29 per cent, and skin petechiae, 64 per cent, indicates an increased capillary permeability. The usual incidence of hemorrhagic disease of the newborn has been shown by Javert and others to be only 0.7 per cent.

The following case illustrates the occurrence of melena as the first indication of erythroblastosis. This case is important in that the mother subsequently delivered an infant with erythroblastosis associated with hemorrhagic diathesis, and previously had delivered an infant with hydrops fetalis.

CASE 3. Mrs. P. S., aged 33, negro, parity 9–8–1–6, delivered a deadborn, macerated and edematous infant in her previous pregnancy; the autopsy showed erythroblastosis. The present pregnancy was complicated by a mild pre-eclampsia. She was delivered in the thirty-eighth week of gestation, after a 2½ hour labor, by breech extraction. This baby weighed 3,820 grams. Soon after birth it developed dyspnea, skin petechiae, facial twitchings, and had a large bloody stool. The liver and spleen were enlarged. The red blood cell count on the first day of life was 4,300,000; hemoglobin, 16 grams; white blood cells, 38,100; 140 nucleated red cells were counted per 100 white cells. Two transfusions were given in addition to supportive therapy, but slight edema of the extremities occurred and the child died 36 hours after birth. The chief pathology comprised: erythroblastosis of the liver and spleen, with many nucleated red cells in the vessels. There was subarachnoid and cerebellar hemorrhage to which death was attributed. The placenta weighed 880 grams and was grossly unremarkable.

Two years later, this mother was delivered of her ninth full term child in the thirty-seventh week of gestation. Again she had a mild pre-eclampsia. This child weighed 4,580 grams. On the first day of life the white blood cell count was 42,000 and there were 4 erythroblasts and 98 normoblasts per 100 white cells. The red count was 6,000,000 for which reason only serum transfusions were given. The child developed slight edema, cyanosis, and many skin petechiae of the face and arms. He made an uneventful recovery.

Essential autopsy data. In general, the hydrops cases showed a greater degree of erythroblastosis and erythroblastemia than did the icterus types, as shown by 29 complete postmortem examinations (88 per cent).

The chief deviation from normal, in addition to the hydrops or icterus, was seen in the heart, liver, and spleen (Fig. 3b). The heart was invariably hypertrophied, and in some cases weighed 40 grams. This hypertrophy caused fetal distress as well as cardiac murmurs, which were heard in 3 infants with icterus and 6 with hydrops; and of the latter, 3 were heard *intra uterum*. Histological section of the heart muscle usually showed vacuolization due to the edematous infiltration.

The liver and spleen were invariably increased in weight and on histological examination numerous hematopoietic foci and sinusoids were seen filled with immature red and white cells (Fig. 5, frontispiece). The foci were often more numerous in the hydrops cases, and have been regarded by Abt as a persistance of embryonal blood formation. Since these infants were more immature than the icterus gravis cases, we feel that prematurity may be sufficient to explain the difference. Deposits of pigment could be seen in the Kupffer and liver cells in the hydrops cases (Fig. 6, frontispiece). The pigment is stained blue in some cells and remains brown in others. This may represent hemoglobin of fetal and adult origin as suggested by Darrow, Nowakovsky, and Austin. The icterus cases usually had no intracellular pigment, but had instead numerous bile thrombi. The livers of several deadborn infants were so autolyzed that histological study was impossible, yet the pigment was readily observed. Its presence may prove of diagnostic importance when tissues are extremely macerated. Many livers showed varying degrees of cloudy swelling, fatty degeneration, or necrosis (Fig. 7a), and these changes together with the intracellular pigment and hematopoietic foci, which constituted from 10 to 40 per cent of the liver structure, made up a liver parenchyma of greatly impaired functional capacity. Degeneration is observed in the livers of infants dying of other causes, but its presence in erythroblastosis, in addition to the hematopoietic foci and intracellular pigment, would speak for impaired hepatic function if the postmortem changes could be definitely ruled out. In general, the histological changes were most marked in the hydrops group. De Lange and Arntzenius found cases without degeneration of the liver, as we have also observed; while others, including Klemperer, and Hawksley and Lightwood, have described the degenerative changes. Subsequent juvenile cirrhosis of the liver may be traceable to icterus gravis according to Boynton and Wyllie, Braid and Ebbs, while Wilson has associated hepatic degeneration with pathology of the lenticular nuclei. Cirrhosis of the liver may be associated with low serum proteins, edema and death, as reported in a 2½ year old girl by Thompson, Ziegler, and McQuarrie. Hypoproteinemia has been regarded by Weech and others as the result of severe liver damage.

Hematopoiesis was usually evident in other organs including the kidney, adrenal, thymus, thyroid, pancreas, and various lymph nodes. The degree of involvement was greatest in the hydrops cases. The kidney sometimes showed cloudy swelling and tubular degeneration in addition to deposits of pigment, which may handicap the child after birth when excretion by the placental route is no longer present.

The serous cavities usually contained amber colored fluid in varying amounts, and this was most marked in the hydrops cases. The abdominal cavity at times contained up to 150 cubic centimeters of amber colored fluid.

Petechial hemorrhages were often seen in the internal organs which, together with the clinical evidence of skin petechiae and hemorrhage diathesis, may be attributed to impaired capillary permeability.

Kernicterus, first described by Schmorl, was observed in 5, or 45 per cent, of the icterus cases and in none of the 9 hydrops cases that came to autopsy. The basal nuclei of the brain, particularly the optic thalamus, olivary bodies and the dentate and lenticular nuclei were involved. Two of the 5 cases that showed the condition had convulsions with no sign of intracranial hemorrhage. Zimmerman and Yannett described a child of 3 years with a history of icterus gravis who had residual spasticity and mental retardation. Degeneration of the basal nuclei was found at autopsy and the possible relation to kernicterus was emphasized. The association of lenticular degeneration and liver cirrhosis was made by Wilson in 1912. Parsons, Hawksley and Light-

wood, Strong and Marks, and others have associated icterus gravis as a possible forerunner of hepatolenticular degeneration.

The epiphyseal line was described as normal in some cases and widened in others, which may indicate metabolic disturbance. There were no histological or roentgenological evidences of syphilis. The bone marrow was hyperplastic and contained many immature cells of the red and white series in varying degrees of maturation (Fig. 7b). The persistence of hematopoietic foci in the liver and organs as well as the bone marrow hyperplasia certainly indicate that there is no lack of antianemic principle required for red cell maturation. It is possible that the immature red cells enter the circulation from the foci located in the various organs and not only from the bone marrow.

Heart blood cultures. These were obtained in 18 infants and were negative in all, confirming the studies of Abt, Diamond and his co-workers, and ruling out sepsis neonatorum.

Cord blood studies. These were made on 5 hydrops cases and 3 infants with icterus gravis, while 11 infants of the latter group were studied on the first day of life and are, therefore, comparable to the cord blood studies. The average of the findings are as follows:

	R.C.C.	Hgb. (gms.)	C.V.	W.C.C.	N.R.C.	Index Vol.	Index Color
5 Hydrops cases..	1,51	5.5	25	54,3	37,6	1.5	1.3
3 Icterus cases....	3,56	14.7	52	42,0	21,2	1.3	1.4
11 Icterus cases on first day of life..	3,1	13.6	..	37,2	18,5	..	1.4

Cord blood studies in erythroblastosis are seldom described in the literature. We have studied smears of cord blood in 9 cases of hydrops and 6 cases of icterus. The average results of these studies are:

	Normoblasts	Erythroblasts	Reticulocytes	Immature polymorphonuclears	Immature lymphocytes	Red cell diameter
9 Hydrops.....	304	98	7.1%	34	16	9.5μ
6 Icterus.....	71	14	.....	10	0	8.0μ

The hydrops cases showed marked macrocytosis and polychromasia, with numerous erythroblasts, normoblasts, mitotic figures, and reticulocytes (Fig. 8). The immature polymorphonuclear cells were abundant, as were lymphoblasts, which confirms the findings of Diamond, Blackfan, and Baty. The volume index (normal 1.08) and color index (normal 1.2) were very much increased in both groups. The mean corpuscular diameter (normal 8.5 μ) was not increased in the icterus group, but was markedly so in the hydrops infants (9.5 μ). The macrocytosis suggests liver damage or insufficiency, for Kracke and Garver, and others find liver disease complicated by a macrocytic anemia. The ratio of normoblasts to erythroblasts in the hydrops group was 3.8:1, and 5:1 in the icterus group. In normal premature infants, according to Javert, it is 6.6:1, and in full term infants 14:1.

The blood studies vary greatly with the clinical type of the disease. In the hydrops type, the red cell count may be as low as 500,000 per cubic millimeter. The nucleated red cells are acetic acid resistant and are, therefore, present in the counting chamber as "white cells," and may number up to 300,000 per cubic millimeter.

Smears stained by the Wright technique (Fig. 9, frontispiece) reveal megalocytic erythroblasts with large nuclei containing a lacy chromatin network and several nucleoli, with a cytoplasm which is basophilic since hemoglobin is deficient or absent. Mitotic figures are frequent. The normoblasts are smaller and approach the red cell in size. They have a cytoplasm which is less basophilic, and the nuclei are smaller and pycnotic. The degree of erythroblastemia varies with the hydrops or icterus types, being more pronounced in the former.

The degree of erythroblastosis seems to control the severity of erythroblastemia, for in the hydrops type in which both are most pronounced, a great many immature red cells —erythroblasts—can be found in the circulating blood. In the icteric form, nucleated red cells are fewer in number and are more mature—normoblasts—while in the anemic form of the disease these cells are even more mature—reticulocytes and normoblasts. Consequently, it is probable that the hematopoietic foci as well as the hyperplastic bone marrow liberate these cells.

In the icterus cases that survived, there was a gradual decrease in the number of nucleated red cells so that in the first week to 10 days of life, they had virtually disappeared from the circulating blood. Therefore, the diagnosis had best be made hematologically at birth or soon thereafter, for it may be missed as in one of our cases in which a normal blood smear was made on the tenth day of life but autopsy revealed unmistakable evidence of erythroblastosis. The rate of disappearance may have prognostic value. Case 4, an infant with hy-

drops surviving 11 days, had 42 normoblasts per 100 white cells on the day of death.

Blood chemistry of the fetus. The chemical constituents of the cord blood per 100 cubic centimeters is presented in the following table:

	Hydrops cases	Icterus cases	Control
Nonprotein nitrogen	(4) 41.7 mgm.	(1) 60.0 mgm.	35.0 mgm.
Uric acid	(1) 7.8 mgm.	(1) 3.8 mgm.	3.1 mgm.
Chlorides	(3) 563.0 mgm.	(1) 395.0 mgm.	500.0 mgm.
Serum proteins	(5) 3.8 gm.	(3) 5.3 gm.	5.9 gm.
Fibrinogen	(2) 0.05 gm.	(3) 0.1 gm.	0.3 gm.
Prothrombin	(2) 5%	(3) 7%	23%
Icterus index	(7) 91 units	(3) 66 units	18 units

(Figures in parentheses denote number of cases studied)

The increased values in the nonprotein nitrogen and uric acid may accompany the higher values observed in the mothers, caused by the pre-eclamptic type of toxemia. The chlorides were elevated in the hydrops group. The serum proteins were decreased in both the hydrops and icterus cases, but to a greater extent in the former, and in 1 case were as low as 1.4 grams. The hypoproteinemia is thought to be the result of liver damage which was the greatest in the hydrops group. Weech has found lowered serum proteins following impairment of liver function in other conditions, and in a case of congenital syphilis.

The prothrombin concentration of the cord blood was studied in 7 cases of erythroblastosis and an average level of between 3 and 7 per cent of normal was obtained. The lowest values were observed in 2 cases with hydrops. The Warner, Brinkhous, and Smith test was employed and, as Javert and Moore have shown, the prothrombin concentration of cord blood is normally about 23 per cent of the adult normal. The hypoprothrombinemia, the lowered serum proteins, the edema and hemorrhagic diathesis, all speak for impaired capillary permeability and may be associated with impaired liver function, being most marked in the hydrops cases.

Rh factor. Determinations made by Levine in 6 cases showed the cord blood to be Rh positive in all. The blood of the fathers and mothers were Rh positive and negative respectively with one exception which will be reported elsewhere.

Differential diagnosis. In addition to the classification of erythroblastosis neonatorum as to type, it is necessary to rule out the following conditions in approximate order of frequency: physiological jaundice; prematurity; intracranial hemorrhage; hemorrhagic disease of the newborn; congenital heart disease; congenital syphilis; sepsis neonatorum; obliteration of the bile ducts; familial acholuric jaundice, Winckel's disease and hypoproteinemia.

Treatment. In addition to the supportive measures such as oxygen infusions and artificial feedings, repeated transfusions were given. As many as 9 transfusions, averaging 60 cubic centimeters in amount, were given in the first days of life. We agree with Arnold and Downey who state that the physician who fails to give enough blood is able to make complete case reports including the autopsy protocol. Hampson has used intramuscular whole blood in icterus gravis with good results, which Hawksley and Lightwood failed to duplicate. The value of whole blood by vein and intramuscularly in addition to the cellular elements may be due in part also to the protein and prothrombin content. For this reason vitamin K may be of value, and we have used it in several cases. The transfusions were given with blood from donors that were compatible. Since the blood of the infants is Rh positive, tests for this factor may also be indicated.

Fetal mortality. In 1937 the author first directed attention to erythroblastosis as an important cause of fetal mortality, stating that it was 2½ times greater than syphilis. It is responsible for more fetal deaths than asphyxia neonatorum, hemorrhagic disease of the newborn, and toxemia of pregnancy. Macklin, Potter, and others have since written on the rôle of erythroblastosis in infantile mortality. In a study of 750 fetal deaths in infants weighing over 1,500 grams, including stillbirth and neonatal deaths up to the fourteenth day of life, 3.2 per cent were caused by erythroblastosis and 1.3 per cent were due to syphilis. Syphilis as such has been overrated as a cause of stillbirths.

The fetal mortality rate in our 47 cases varied with the type of erythroblastosis encountered. Of this number 70 per cent perished.

Type of erythroblastosis	Still or dead-born	Number of deaths: Neo-natal	Total	Percentage
Hydrops (16 cases)	9	7	16	100
Icterus (22 cases)	1	11	12	54
Anemia (3 cases)	0	1	1	33
Hemorrhagic diathesis (3 cases)	0	1	1	33
Unclassified (3 cases)	2	1	3	100
Total	12	21	33	70

The mortality rate was 100 per cent in the hydrops cases although 1 infant survived for a period of 11 days (Case 4). The rate for the icterus cases is about 50 per cent, which agrees with the observations of Hellman and Hertig. Of the unclassified cases, death was due to prolapsed cord and intrapartum infection in 2 cases, while the third case was one of twins here reported (Case 2).

The following case is unusual in that the infant with hydrops fetalis survived 11 days. Wolfe and Neigus report 6 days, Hellman and Hertig 2 days, as the longest period of survival.

CASE 4. Mrs. D. T., aged 31 years, American Hebrew, parity 2–0–3–2, in whom two spontaneous abortions occurred between her first and last full term infants, which are alive and well. The present pregnancy was complicated by "hydramnios"; the uterus measured 39 centimeters at term (41 weeks gestation). Delivery was effected with forceps, the indication for which was fetal distress in the second stage of labor. The baby was excessive in size, weighing 4,380 grams, part of which was due to subcutaneous edema. The child required simple resuscitation at birth. The placenta weighed 1,760 grams. No histological section was made. The amniotic fluid was described as greenish yellow. The mother sustained a blood loss in the third stage of 660 cubic centimeters, part of which was due to a laceration into the right broad ligament because of dystocia due to difficulty with the shoulders.

Because of the edema of the infant, hematological studies were made at once. The red count was 5,200,000 per cubic millimeter; hemoglobin, 14.6 grams; white count 6,400, of which 3,400 were nucleated red cells; 86 nucleated erythrocytes, including erythroblasts, were counted per 100 white cells. The bleeding and clotting times were normal. On the subsequent day the serum proteins were 5.0 grams per 100 cubic centimeters, the blood calcium was 11.6, phosphorus 6.5, cholesterol 131, urea nitrogen 33 milligrams, chlorides 591 milligrams per 100 cubic centimeters. On the third day of life, definite jaundice developed (icterus index 100) and the edema seemed to be increasing. Petechiae developed on the face, and attacks of dyspnea and cyanosis were frequent. In addition to the usual supportive measures, the child was given 8 transfusions (total 405 c.cm. citrated blood) and despite this, the red blood cell count was 4,900,000 and the hemoglobin 14 grams on the day of death. Nucleated red cells persisted in the blood stream and on the day of death there were 42 nucleated red cells per 100 white cells in the circulating blood. The nucleated cells disappear in 4 days in normal infants according to Javert and about 10 days in infants with erythroblastosis. The rate of disappearance may have prognostic significance.

Autopsy revealed the presence of greenish yellow fluid in the pericardial (7 c.cm.), pleural (10 c.cm.) and abdominal (50 c.cm.) cavities. The heart was enlarged, weighing 45 grams, the liver weighed 203 grams, the spleen 10 grams. The liver and spleen showed diffuse erythroblastosis, the liver having in addition, fatty degeneration and portal fibrosis. Hematopoietic foci were also seen in the adrenal and kidney. Petechial hemorrhages were observed in the heart, thymus, adrenal and lungs. The bone marrow showed erythroblastic and granulocytic hyperplasia. Blood culture and Kline reaction were negative.

ANTEPARTUM DIAGNOSIS

This study has been presented for the most part from the obstetrical point of view and only the pertinent pathological and pediatric features have been discussed. Our aim has been to feature certain criteria which may prove helpful in making a correct antepartum diagnosis. This has obvious importance in the obstetrical management of the mother. For instance, in Case 5 patient was very anxious for a cesarean section in order to give the child every opportunity for survival, for several physicians had so advised her. The presence of an infant with hydrops was proved and section was refused.

CASE 5. Mrs. L. H., aged 34 years, white, parity 2–0–2–0, with a history of two abortions and two previous infants with hydrops, was first seen in the twenty-eighth week of gestation. A hematological examination revealed a normocytic hypochromic anemia for which iron was prescribed. The serum proteins were reduced and averaged 5.2 grams per 100 cubic centimeters, the plasma fibrinogen was only 0.3 gram per 100 cubic centimeters, while the prothrombin was 100 per cent of normal. The patient was placed on a high protein diet, rich in vitamins.

In the thirty-fifth week of pregnancy, the height of the uterus measured 36 centimeters and "hydramnios" was suspected. At this time a fetal bruit became evident. The patient remarked that the fetal activity was not great. Ankle edema became a prominent sign and a low protein diet was ordered. There was a gain of 4 kilograms in the following week. The blood pressure, which had been normal previously, rose suddenly to 170/100 and remained at that level, while albuminuria developed. At this time, the patient was hospitalized for study and treatment. The blood chemical findings included a uric acid reading of 7.4 milligrams per 100 cubic centimeters and a carbon dioxide combining power of 36.2 volumes per cent. Intravenous glucose was given. An x-ray examination of the fetus was made, a soft tissue technique being used in order to show soft tissue edema. A suggestive halo was observed about the child's head. However, the Buddha or frog-like posture of the infant was found to be more definite (see Fig. 10b).

In the meantime, the maternal blood pressure increased to 180/110, the albuminuria persisted although the edema improved. In view of the toxemia and the increased hazard to the infant, the patient and her husband clamored for delivery by cesarean section. However, by this time sufficient data had been collected, namely, obstetrical history, hydramnios, fetal heart murmur, toxemia, and x-ray evidence of edema in the infant, all of which pointed to a diagnosis of erythroblastosis fetalis of the

hydrops type. The parents' request for cesarean section was refused. Instead, the membranes were ruptured artificially (the uterus being very irritable) and after a short labor of 6 hours, a midforceps delivery was effected with the pediatrician in attendance. The placenta was very large and edematous with a pale maternal surface, very friable, and was delivered with difficulty because of its large size (2,100 grams). A blood loss of 1100 cubic centimeters was sustained in the third stage of labor. Postpartum course was uncomplicated.

The child weighed 3,020 grams (excessive for 37 weeks' gestation), part of which was due to marked generalized edema. He lived for 15 minutes during which time resuscitation with carbon-dioxide-oxygen mixture was carried out. Fluid was also aspirated from the thorax and abdomen to remove these obstacles to respiration, and blood was obtained from the cord for cross matching and blood studies. The red cell count was 1,000,000 per cubic millimeter; hemoglobin, 31 per cent (Sahli); white cell count 9,600 per cubic millimeter; of which 6,930 were nucleated red cells. The red cell volume was 15 millimeters per cent. The volume index was 1.6 and the color index 1.5, and the mean corpuscular diameter was 10.7 μ. In the stained smear, 130 normoblasts and 30 erythroblasts were counted per 100 white cells. Many of the latter were immature, and 6.2 per cent of the red cells were reticulocytes. The plasma prothrombin was less than 5 per cent of normal, the serum proteins were only 1.41 grams, and the nonprotein nitrogen was 41.7 and the uric acid 7.8 milligrams per 100 cubic centimeters. The icterus index was 75 units. Autopsy and histological examination confirmed the diagnosis of erythroblastosis fetalis.

This patient became pregnant 6 months later and a therapeutic abortion was performed because of residual renal and liver damage following the severe pre-eclampsia. The history of 3 infants with erythroblastosis may have contributed to the decision to terminate the pregnancy, although it was not used as the indication. At this time studies of the Rh factor revealed the mother to be negative and the father to be positive. The patient has since adopted a child. This case also illustrates the gloomy obstetrical future of primiparas having a firstborn infant with erythroblastosis as discussed above under "Familial History."

There are cases that have a normal course until labor begins and then developments occur, such as loss of fetal movement, irregular fetal heart, premature rupture of the membranes with escape of yellow fluid, etc., which should arouse suspicion. Diagnosis at this stage of pregnancy is illustrated by the following case referred to in the preliminary report of this study made in 1937.

CASE 6. MRS. N. J. was a 29 year old Armenian woman, parity 1–0–0–1, with a negative Wassermann. The pregnancy was uneventful until the thirty-ninth week of gestation when the membranes ruptured prematurely, and it was observed that the fluid had a golden yellow color. The head was dipping well into the pelvis, the cervix was closed and there were no uterine contractions. The fetal heart was slow with a rate of 60 to 80 per minute. As contractions developed, the rate increased. However, rectal ether without quinine was given in order to relax the uterus between pains. Spontaneous delivery occurred after a labor of 9 hours.

The infant was a female weighing 3,340 grams. The vernix had a golden yellow color, and the child had a suggestive Mongoloid appearance. There was localized edema of the eyelids. Resuscitation with carbon-dioxide-oxygen mixture was necessary. The cord blood was promptly studied and 80 normoblasts and 20 erythroblasts were counted for 100 white cells. The red count was 5,600,000 and the white count 80,000 of which 40,000 were nucleated red cells. Despite a prompt diagnosis and a transfusion of 60 cubic centimeters of compatible blood, the infant died 3 hours after delivery. Autopsy confirmed the clinical diagnosis. The placenta weighed 660 grams, had marked yellow color of the membranes, and histologically was remarkable only in that the nucleated red cells were increased in the fetal vessels.

A correct antepartum diagnosis of erythroblastosis neonatorum was made correctly by the author in 8 out of 10 cases. The signs having the greatest value in the 10 cases in which intrauterine diagnosis was attempted are as follows: multiparity, 10 cases; excessive uterine enlargement ("hydramnios"), 6; amniotic fluid, yellow-brown, 6; premature labor, 6; nationality (Irish), 6; icterus index increased, 5; erythroblastosis in a previous infant, 4; toxemia of pregnancy, 4; fetal distress, before or during labor, 3; intrauterine death of the fetus, 3; systolic bruit of fetal heart heard in the uterus, 3; aspiration of cord blood before delivery (prolapsed cord), 1; x-ray examination of fetus while within the uterus (7 cases studied), 2.

To recapitulate, multiparity and excessive uterine enlargement beyond the duration of gestation were valuable criteria, while the previous obstetrical history was less important. The x-ray was found to be among the

least valuable aids. Its use is limited to the hydrops cases. We took our first roentgenogram in May, 1936, in an effort to detect edema of the scalp. It was not successful. Subsequently, we have studied 7 cases; 2 proved to have infants with icterus, and 5 with hydrops. The edema of the scalp, or so called "halo" as reported by Hellman and Irving in 1938, was seen in only 2 hydrops cases (see Fig. 10a). However, these and other cases showed a Buddha or frog-like habitus of the child which may be attributed to the enlarged fetal abdomen and hydrothorax (Fig. 10b). The roentgenogram in another case revealed a very large placenta. The large placenta together with fetal movements within the uterus makes roentgenological demonstration of the "halo" and fetal habitus rather difficult. We have come to place greater reliance on the Buddha position and recommend anteroposterior and lateral plates to show the posture of the child in suspected hydrops cases.

Antepartum diagnosis may be facilitated by maternal and paternal blood studies for the Rh factor if the results are interpreted with the history and clinical data presented.

PATERNAL STUDIES

In a recent report, Otto stated that 5 cows serviced by the same bull had 5 hydropic calves. When sired by a different bull, the same cows delivered normal calves. With this information in mind, 6 fathers of infants with erythroblastosis (4 hydrops and 2 icterus) were studied. The semen examination revealed a total average volume of 3.7 cubic centimeters with an average of 88 per cent normal sperm, which compares favorably with the values for healthy males as stated by Cary, who made these studies. The genitalia were not abnormal. One father had a cleft palate. The Wassermann reaction was negative in all. Complete blood studies were entirely normal except for a slight deviation from normal in the differential count. These fathers were Rh positive, with 1 exception.

From the evidence at hand, and since sterility is not a factor, it must be concluded that the male is not directly responsible. Artificial insemination or remarriage may shed light on the subject, except that we have had 4 women with previous erythroblastosis bring forth 4 healthy infants without changing their mates.

ANTEPARTUM AND INTRAPARTUM TREATMENT

Intrauterine diagnosis of erythroblastosis is important so that proper therapy can be instituted in order to prevent the condition. The marked diminution of congenital syphilis following antiluetic therapy is an example of what can be accomplished by specific antepartum medication. It is hoped that specific therapy will be discovered for erythroblastosis. We have employed in turn a high protein, high vitamin diet, iodine, and iron, vitamin B_1, Brewer's yeast, calcium and injections of liver, vitamin B complex, 'copperin A' and calcium, without affecting the outcome. Bonney and Morton used potassium chlorate, calcium, and wheat germ antenatally, but the infant had erythroblastosis. From this evidence, it appears that a well balanced dietary regimen does not prevent the development of the disease in the unborn child.

The evaluation of any antepartum therapy is difficult since we have had 4 mothers give birth to normal infants following a previous child with erythroblastosis without special treatment. We have treated 3 mothers with frequent injections of synthetic vitamin K (thyloquinone) during the antenatal period; they having had previous infants with erythroblastosis, and each delivered a child with the icterus type of the disease, one of which died.

Antepartum transfusions have been considered on the basis that if they are of benefit to the child after delivery, they may be of value before delivery. We have had no experience with this procedure.

The induction of premature labor has been advocated by Diamond in order to remove the child from its pernicious environment, and also so that transfusions can be given promptly. We do not agree with this procedure because there is no adequate method for inducing labor without added risk to the infant. Furthermore, prematurity in an infant with erythroblastosis is undesirable, for the hydrops infants are often a month or more before term, and they have a mortality rate of 100 per cent, while the icterus gravis infants are at or near term and have a lower rate of 54 per cent.

Dystocia during the delivery may occur due to the ascites or to difficulty with the shoulders especially when the infant is unduly large. Delivery in Case 4 resulted in a broad ligament laceration because of shoulder dystocia.

Infants delivered by cesarean section have been reported in the literature by Bonney and Morton, A. F. Abt, and Pallos, with the delivery of hydropic or icteric infants. This procedure is condemned except when maternal indications justify it, and should never be performed in order to improve the chances for the baby because of the high fetal mortality. We performed the operation on two occasions, each time for a definite maternal indication.

Asphyxia within the uterus and asphyxia neonatorum were frequent and resuscitative measures immediately after delivery were often necessary. Therefore, the use of analgesia and anesthesia during labor and for delivery should be avoided. If necessary, an episiotomy can be performed, local infiltration with novocain being used. The dyspnea and cyanosis seen after delivery is further evidence of faulty oxygenation due to anemia, hydrothorax, and ascites.

Therapeutic abortion was never performed in mothers with previous erythroblastotic infants, on that indication alone. However, it was a contributing factor in Case 5. However, with the recurrence at 50 per cent for mothers who developed erythroblastosis in previous pregnancies, and nearly 100 per cent when the first born is affected, erythroblastosis should receive attention from this point of view. In certain instances, contraception and adoption of a child may be desirable.

Artificial insemination is frowned upon because of the increasing incidence of erythroblastosis once it has appeared, and because paternal investigation has revealed no abnormality. Furthermore, in Hilgenberg's case, a mother had several normal children by her first husband and after remarriage had babies with icterus gravis. In Smith's case, a man with a normal child by his first wife had children with icterus gravis by a second wife. However, artificial insemination with donor and recipient of the same blood group and Rh negative seems to merit investigation.

PATHOGENESIS OF ERYTHROBLASTOSIS

Many investigators, including Parsons, Hawksley, and Gittins are of the opinion that hemolysis is the precursor of the erythroblastemia, and that erythroblastosis is of secondary development. Abt, von Gierke, Salomonsen, and Clifford and Hertig regard the erythroblastosis as primary and a persistence of the embryonic type of blood formation. In fact, Abt states that any theory must begin by explaining the hematopoiesis. Josephs doubts that erythroblastosis is primarily a disease of blood formation, since the blood returns rapidly to normal in the first 3 weeks of life. The erythroblastemia and erythroblastosis are probably secondary phenomena, since they exist in other conditions such as congenital syphilis, sepsis neonatorum, and even in premature infants, as well as in infants without hydrops, icterus, anemia, or hemorrhagic diathesis.

It is futile to argue as to whether hematopoiesis and red cell hemolysis are primary or secondary characteristics; both are present. Diamond, Blackfan, and Baty regard erythroblastosis as a metabolic disturbance of the hematopoietic system. Darrow concludes that an antigen-antibody reaction explains the pathological processes, i.e., the abnormal red cell destruction, the erythropoiesis, and the hepatic injury and dysfunction. She believes that the placenta transmits the agent from the mother to the fetus. Levine and co-workers reverse the mode of transmission and theorize that when an Rh negative mother becomes pregnant by an Rh positive father, isoimmunization of the mother takes place. Hemolysis may then be initiated in the fetus by the passage of anti-Rh agglutinins through the placenta. This theory is very attractive and merits much more investigation which is in progress at the present time.

The disease may begin as a dysfunction of the liver. What is the evidence to justify this point of view? The hydrops and icterus infants showed histological evidence of liver impairment as indicated by the varying degrees of hematopoiesis, deposits of intracellular pigment, and actual degeneration and necrosis of the hepatic cells. Too much emphasis cannot be given the latter findings because of postmortem changes. There was also physiological evidence of liver insufficiency, since the infants showed hypoproteinemia, hypoprothrombinemia, a high icterus index, and a macrocytic anemia. The patent ductus venosus must also be considered. Finally, the

anlage defect which has been postulated for the hematopoietic system can be applied to the liver, for when the child recovers, the hematopoietic system is normal, but there is evidence of residual liver damage. The high incidence of congenital anomalies in our cases makes anlage defect very plausible.

What happens? The liver fails to produce an adequate amount of serum proteins and prothrombin. In some instances this is severe enough to result in universal edema. The capillary endothelium becomes impaired and multiple petechiae, ecchymoses, and hemorrhagic diathesis occur. There is no apparent lack of antianemic principle judging from the hyperplastic state of the bone marrow. However, anemia develops probably because of excessive red cell hemolysis, and is probably initiated by the passage of anti-Rh agglutinins from the mother to the fetus. This goes on for a long time before birth as indicated by the large amounts of pigment deposited in the liver and other organs. This may also represent a failure of the diseased liver to metabolize the bilirubin, and the icterus index rises. Hyperbilirubinemia is also found in normal newborn infants either with or without physiological jaundice according to Waugh and his co-workers. Most authorities regard hyperbilirubinemia as of hematogenous and hepatogenous origin. In erythroblastosis both mechanisms form a vicious cycle and the damaged liver cannot care for the increased amounts of bilirubin, and it may pass into the maternal circulation and elevate the icterus index of the mothers as was frequently observed. When the infant is placed on its own resources after the umbilical cord is ligated, the icterus index of the infants with icterus gravis rose from 86 to 100 units and in subsequent days increased even further to 150 to 400 units. Anemia develops either within the uterus or after delivery. The diseased liver evidently cannot store adequate amounts of antianemia principle as Kracke and Garver state that it normally does. The physiological and pathological changes were invariably most marked in the hydrops infants having a fetal mortality of 100 per cent and were much less pronounced in the icterus infants, which probably accounts for the better survival rate in these infants.

The views of the older investigators that maternal nephritis and cirrhosis of the liver caused fetal hydrops again bear scrutiny. The increased incidence of pre-eclampsia and eclampsia with liver changes in the mothers and definite evidence of liver impairment in their infants with erythroblastosis suggests a common etiology for both. Pregnancy is necessary for the development of toxemia as well as for erythroblastosis. Parsons, Hawksley and Gittins, and de Lange and Arntzenius believe that a toxic agent is responsible for both conditions. Is it possible that the anti-Rh agglutinin of Levine, Katzin, and Burnham is the agent initiating erythroblastosis and toxemia of pregnancy?

CONCLUSIONS

1. A classification of erythroblastosis dividing the cases into hydrops, icterus, anemia, hemorrhagic diathesis, and *unclassified* types is presented.

2. The total incidence of erythroblastosis was 1:438. The total fetal mortality caused by the disease was 3.2 per cent.

3. Multiparity was an associated factor in 92 per cent of the mothers.

4. A high incidence of pre-eclamptic type of toxemia was found in the mothers of hydrops cases, and to a less extent in the icterus cases.

5. The excessive uterine enlargement, out of proportion to the duration of pregnancy, was shown to be due to the combined weight of the infant and placenta, and not to the "hydramnios."

6. The hydrops infants were born a month or more prematurely, whereas the icterus infants were nearer term.

7. Asphyxia, either within the uterus or after birth, or during the neonatal life, was a prominent symptom in the fetus. For this reason, if erythroblastosis is suspected before delivery, all analgesia and anesthesia is interdicted. Local infiltration can be used for an episiotomy.

8. The incidence of postpartum hemorrhage was increased, particularly in the hydrops group.

9. The incidence of operative delivery was 56 per cent; the chief indication was fetal distress.

10. When the fetus is macerated, histological examination of the placenta and of the liver by means of special pigment stains offers a good opportunity for diagnosis.

11. The obstetrical history of the patient should replace the "family history," since the disease is not familial in the strict sense.

12. The degree of parity is important in predicting a subsequent case of erythroblastosis. The incidence of erythroblastosis in pregnancies after its initial appearance is approximately 50 per cent. If the first-born had the disease, the incidence for subsequent infants is nearer 100 per cent.

13. Case histories of hydrops and eclampsia, identical twins with erythroblastosis, erythroblastosis with hemorrhagic diathesis as the initial symptom, hydrops with survival for 11 days, icterus gravis diagnosed *intra uterum* and hydrops fetalis diagnosed *intra uterum* were presented.

14. Maternal blood studies were usually normal save for an increased icterus index and uric acid, probably due to maternal liver damage accompanying toxemia. The serum proteins were generally reduced. Several of the mothers were Rh negative.

15. The infants had a high incidence of congenital anomalies.

16. Autopsy often revealed some degree of liver degeneration, pigment deposits, and hematopoiesis, which were usually most marked in hydrops cases.

17. Complete studies of cord blood are presented. The number of erythroblasts and normoblasts, as well as their ratio, are important diagnostic criteria.

18. The serum proteins and the prothrombin concentration of cord blood were reduced especially in the hydrops cases, while the icterus index was greatly increased, also to a greater extent in the hydrops group. These changes together with the macrocytic anemia are interpreted as physiological evidence of impaired liver function.

19. The immediate treatment of erythroblastosis is to combat asphyxia. Repeated transfusions from a compatible donor, in order to provide protein, prothrombin, and blood cells for the infant, are imperative.

20. The mortality for the hydrops cases was 100 per cent, for the icterus group, 54 per cent.

21. Correct antepartum diagnosis was made in 8 of 10 attempts and the important criteria were stated.

22. The Buddha-like habitus of the fetus *in utero*, by x-ray examination, is an important diagnostic feature.

23. Paternal studies including blood and semen failed to disclose any abnormality. Several fathers were Rh positive, except in one instance.

24. The management of a patient with suspected erythroblastosis is given. Cesarean section should not be performed except for maternal indication.

25. The probable pathogenesis of erythroblastosis is presented on the basis of liver dysfunction. Anatomical and physiological evidence is given to support this view. The significance of the Rh factor was mentioned.

26. Erythroblastosis runs part of its course *in utero* and the obstetrician and pediatrician in consultation are in a strategic position for antepartum diagnosis.

27. Hematological studies of the cord blood afford a prompt and simple method of making the diagnosis at the time of the delivery, so that treatment may be instituted promptly.

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TREATMENT OF FRESH TRAUMATIC AND CONTAMINATED SURGICAL WOUNDS

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IN the evaluation of a method of management of fresh contaminated wounds three questions must be answered. Does the method render the wound aseptic? If not, does the method injure the tissues and thereby interfere with the normal mechanism of defense against infection and of repair? And third, the all important one: What are the clinical results of the method? In the report which follows an attempt is made to answer these questions.

We believe that there is ample experimental and clinical evidence that no method in use today renders a contaminated wound absolutely free of bacteria. As a matter of fact, surgical asepsis is never absolute, and even in so called sterile operative surgery the sterility is always relative. Therefore, the question as to whether a given wound remains aseptic or becomes infected and suppurates depends upon two factors: the quantity and the character of the micro-organisms which remain in the tissues and the effectiveness of the defense mechanism.

We also believe that there is ample experimental and clinical evidence that the chemical bactericidal agents, which are so generally used to "disinfect" wounds, destroy or devitalize the tissue cells with which they come in contact and thereby seriously impede the inflammatory response and impair the effectiveness of the natural mechanism of defense.

If the bactericidal agents always rendered wounds free from bacteria, the injury inflicted upon the tissues would be of little consequence. However, failing to destroy all the microorganisms, they leave the tissues damaged and less capable of coping with the bacteria which remain viable.

Both from experimental and clinical evidence accumulated by us and from similar data reported by others, we believe that wounds can be rendered as relatively sterile by mechanical washing with very copious irrigations of isotonic salt solution as by the application of bactericidal agents. This method has the very important advantage that it leaves the tissues essentially uninjured, to mobilize the natural defenses to deal with the microorganisms which remain.

An abundance of evidence has accumulated to establish the sulfonamides as very effective bacteriostatic agents for certain bacteria. From the experimental data reported by others and from that which follows it is apparent that sulfanilamide applied directly to the tissues causes no apparent damage to the cells and does not alter the normal course of repair of either bone or soft tissues. Actually in our animals it facilitated repair in contaminated wounds by preventing infection.

EXPERIMENTAL OBSERVATIONS

1. Tissue response to application of sulfanilamide, normal salt solution, and a few of the antiseptic or bactericidal preparations most commonly employed. In each of 4 rabbits 5 small transverse incisions were made into the subcutaneous tissue of the abdominal wall on each side of the midline at regularly spaced intervals. Rigidly aseptic technique was employed. One wound served as a control. One was washed vigorously with isotonic salt solution. The 8 remaining were painted thoroughly with one of the 8 agents: tincture of green soap, ether, alcohol, tincture of iodine, sulfanilamide powder, and solutions I, II and III. The unnamed solutions are the commercial preparations most widely used in the United States. The wounds were closed with adhesive tape and covered with sterile dressings.

In a second series of 8 rabbits approximately 5 minims of each of the 9 test agents was injected into the subcutaneous tissues of the abdominal wall with hypodermic needles. Points of injection were marked with India ink.

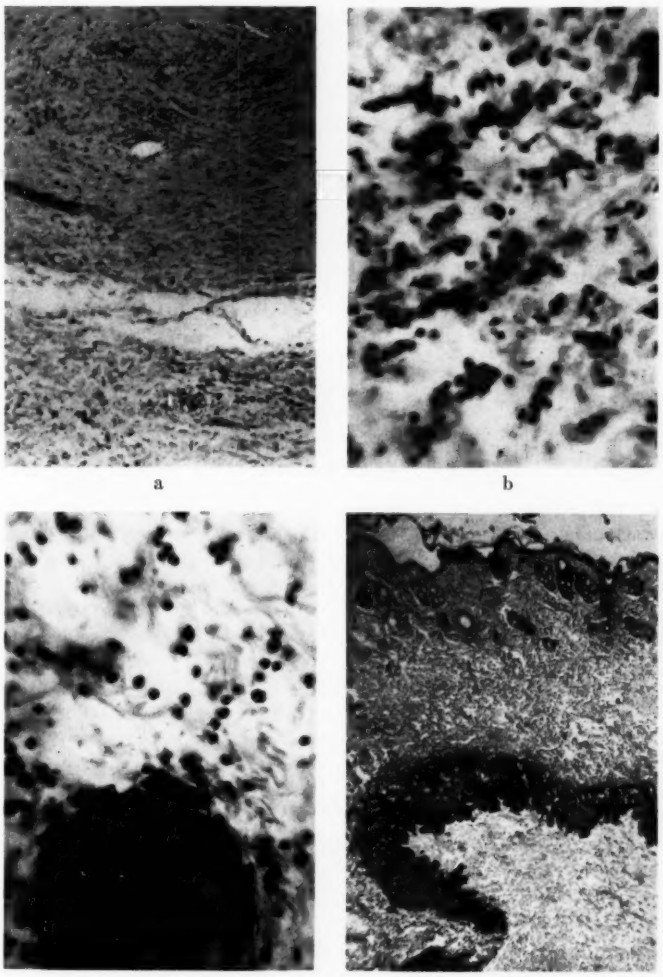

Fig. 1. a, Mild inflammatory response 12 hours after 5 minims of ether had been injected into the tissues. Note slight edema and leukocytic infiltration. b, A high-power magnification of a shows swollen tissue cells with poorly staining nuclei. c, Moderate inflammatory reaction 4 hours after injection of alcohol. Note moderate edema, round cell infiltration, pale staining tissue cells and a thrombosed blood vessel. d, Gross tissue necrosis and severe inflammatory response (abscess) at the site of injection of 5 minims of the tincture of green soap. Injection made 12 hours previously.

One animal in the first series and 2 in the second were sacrificed at each of four intervals following incision or inoculation, 4, 12, and 48 hours and 5 days. Blocks of skin and subcutaneous tissue containing the sites of incision or inoculation were excised and studied microscopically. Normal salt solution provoked essentially no more tissue damage or inflammatory response than did mere trauma as measured by the controls.

Similarly, there was no evidence that sulfanilamide injured tissue cells or that it incited more than a feeble inflammatory response. All of the other agents consistently gave rise, in various degree, to tissue reaction to injury. Curiously, ether was the least, and green soap the worst, offender. The latter produced gross tissue necrosis with abscess formation in more than half of the specimens. Antiseptics II and III also were provocative of gross necrosis and abscess formation. Although iodine and alcohol caused moderate to marked inflammatory reactions no gross evidence of necrosis was found in the specimens.

Photomicrographs of specimens illustrating degrees of tissue reaction appear in Figure 1.

II. Contaminated compound fractures. In 18 rabbits segments of both radial shafts measuring approximately 0.5 centimeter were removed subperiosteally and filled with constant broth suspensions of hemolytic streptococci, hemolytic colon bacilli and Staphlococci albi. The latter two cultures were obtained originally from infected wounds of rabbits.

Four animals were used as controls and after inoculation the wounds were closed without further treatment. Two of these animals died within a few days; the 2 others developed abscesses at the operative sites in both legs, which drained for many days. Only 1 of the 4 fractures developed union and this was rather meager. In 2 fractures segments of the shaft had obviously been sequestrated. In the 14 remaining animals the wounds were inoculated with the cultures, closed for 10 minutes, and then re-opened and filled with the test agents and antiseptic solutions used in experiment I. Thus 2 rabbits were utilized for each antiseptic agent.

A brief summary of the results in these 14 animals follows, and illustrative roentgenograms appear in Figure 2.

1. Wounds lavaged with salt solution and filled with sulfanilamide powder. 4 wounds—no infection and all healed by primary intention. 4 fractures—all healed normally with bony union.

2. Sulfanilamide only: 4 wounds—2 healed by primary intention, 1 mildly and 1 grossly infected. 4 fractures—in all, bone repaired normally.

3. Ether: 4 wounds—all infected, 2 grossly. 4 fractures—2 failed to unite and 2 partially repaired.

4. Alcohol: 4 wounds—2 grossly infected (one in each rabbit). 2 fractures—both failed to repair. 1 rabbit died after 5 days—autopsy findings of consolidated lungs.

5. Tincture of iodine: 4 wounds—2 grossly infected and 2 superficially infected. 4 fractures—3 totally ununited and 1 partially repaired.

6. Antiseptic I: 4 wounds—2 grossly infected (one in each animal). 2 fractures, one totally ununited and one partially repaired. 1 rabbit died after 3 days, no definite cause of death demonstrable.

7. Antiseptic III. 4 wounds—3 grossly and 1 superficially infected. 4 fractures—4 non-unions.

8. Tincture of green soap: 4 wounds—all grossly infected. 2 fractures—both failed to repair. One rabbit died after 10 days from a diarrhea and inanition.

III. Influence of the topical application of sulfanilamide upon the repair of bone and soft tissues. In 12 rabbits the radius of each leg was exposed and fractured by a transverse saw-cut. The wound of each left leg was closed to serve as a control; that of each right leg filled with powdered sulfanilamide and closed tightly. Two rabbits died and there were 2 grossly infected wounds of the control legs.

The animals were killed and the specimens recovered for x-ray and microscopic study, 2, 3, 4, 5, and 6 weeks after operation.

There was no gross or microscopic evidence of any difference in the rate or character of the repair of either the soft tissues or the bone in the control as opposed to the sulfanilamidized wounds. A comparison of the progress of bone repair is shown in Figure 3.

EXPERIMENTAL RESULTS

From these studies certain deductions can be made and although these deductions alone are not necessarily clinically applicable, they would seem to become so when supported by similar, if not identical, clinical observations.

It is apparent that the commonly used bactericidal or antiseptic solutions did not render all wounds completely free from bacteria; and furthermore, that these agents caused injury to the tissues varying from edema with minor cell death to gross necrosis of the tissues. It is also apparent that these solutions caused interference with the repair of bone, presumably the result of devitalization of the osteogenic elements. It is noteworthy that ether

Fig. 2. Fractures of the radius induced by resections of 0.5 centimeter segments of the shafts. Wounds inoculated with cultures of hemolytic streptococcus and colon bacillus and Staphylococcus aureus. Roentgenograms at 6 weeks. From left to right: 1, Control—Wound grossly infected, an associated osteomyelitis with sequestration followed by union with a thin bridge of new bone. 2, Tincture of green soap—Suppuration, no new bone, non-union. 3, Antiseptic I—as in 2. 4, Iodine—as in 2 except proliferation of new bone. 5, Alcohol—suppuration but proliferation of new bone with some union of fragments. 6, Saline irrigation and sulfanilamide—no infection and good bony union.

caused relatively little injury to tissues and tincture of green soap severe tissue damage.

Although sulfanilamide caused some edema response in the tissues it was relatively innocuous and there was no evidence that it altered the normal course of repair of either soft tissue or bone. Key and Burford likewise found no evidence of retardation of healing of uninfected fractures and soft tissue wounds in animals as a result of local implantation of sulfanilamide.

Sulfanilamide was very effective, but not completely so, in preventing infection in wounds grossly contaminated with specifically pathogenic micro-organisms. These observations confirm those of Jensen et al., and of Key and Burford. The latter found sulfanilamide more effective than the other sulfonamides.

In the animals in which the contaminated wounds were thoroughly washed with salt solution before sulfanilamide powder was applied, infection was entirely eliminated. It is our impression that the thorough washing of the wounds with salt solution disposed of most of the bacteria and was the more important step, while sulfanilamide, as a bacteriostatic agent, contributed an additional safeguard. Furthermore, there was no evidence that either agent used singly or both used jointly caused any damage to tissues.

CLINICAL OBSERVATIONS

Irrespective of the results obtained from animal investigation the merits of a method of

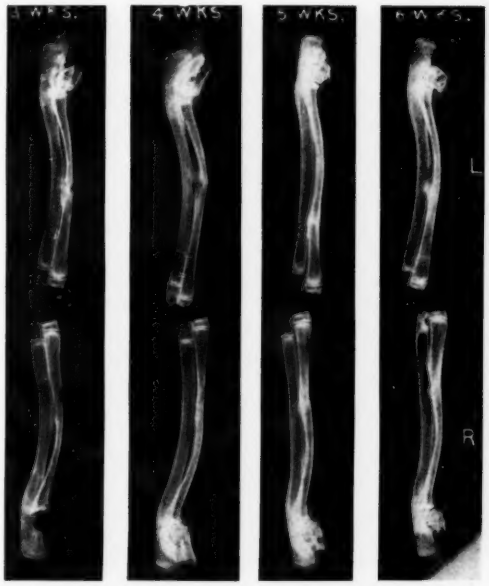

Fig. 3. In these animals the topical application of sulfanilamide powder (lower row) did not alter the rate and completeness of fracture repair as compared to controls (upper row).

treatment can be determined with finality only through clinical application. Therefore, in the way of final judgment a brief report of the results obtained in 25 consecutive cases with major fresh wounds follows:

In 20 of the 25 cases there was good evidence from history or by fact that soiling of the wounds had occurred either by penetration of a foreign body or by exteriorization of bone. All of these patients were treated by us within 8 hours of the time of injury and in general all received the same type of treatment. It consisted of:

1. *Rapid preliminary treatment of shock* in all cases so afflicted. Plasma being unavailable, blood transfusions were used freely for this purpose.

2. After alleviation of shock an *evaluation of extent of injury* was made, including roentgenograms and detailed examinations for evidence of loss of function of individual tendons and nerves.

3. *Cleansing and débridement.* In the compound fractures in which one of the fragments protruded through a laceration of the skin, no attempt was made to replace this fragment until it had been thoroughly cleansed. We believe that this principle should be followed whenever facilities for thorough cleansing are immediately available. A fragment which has been exteriorized is always soiled and the soft tissue bed from whence it emerged is often either totally or relatively sterile. Therefore, cleansing the fragment before replacing it accomplishes the major act in preventing infection and also avoids contamination of the soft tissues. Before the exteriorized fragment was cleansed the skin for a wide area about the wound was rendered surgically clean by scrubbing it with a sterile hand brush for 3 or 4 minutes with a stream of sterile water and green soap constantly flowing over the area. The bone was then washed by gentle brushing of all surfaces with a new sterile brush, while normal salt solution (and only salt solution) was constantly poured over it. Solutions other than saline such as soap and antiseptics were used only in preparing the skin.

In those cases in which the soiled fragment had been replaced before the patient came into our hands, we exteriorized this fragment after the skin had been cleansed and washed it as described.

In either case before the fragment was replaced all parts of the wound were irrigated with large quantities of normal salt solution. It must be emphasized at this time, as it will be repeatedly, that these irrigations must be copious, many liters of saline being used. The wound should be retracted as necessary to expose its entire extent, and all surfaces should be gently agitated with gauze while the solution is flowing over them.

The fragment was then replaced and all torn and devitalized bits of fat, muscle, and fascia were excised. Because crushed skin does not heal readily and often separates, the crushed and devitalized margins of the skin flaps were excised whenever feasible. The wound was then again copiously irrigated with normal salt solution, its surfaces covered with a thin layer of sulfanilamide powder, and the skin closed, usually without drainage.

The fractures were reduced through the open wound in some instances and after skin closure in others. It is our opinion that if these fractures have been thoroughly cleansed and prepared as here outlined, they may be handled essentially as clean simple fractures. This applies to the use of metallic and other foreign material for internal fixation. Whenever indicated we have made use of internal fixation and have had no occasion to regret it.

The technique of cleansing compound fracture wounds in which there was no protruding fragment, and of all other types of wounds, differed only in respect to one important detail. This, the initial step, consisted of closing the wound temporarily with Michel clips to prevent soiling it while the skin was being prepared. This not only prevented the dirty wash water from running into the wound but also permitted scrubbing across the approximated skin edges. After the skin had been rendered surgically clean, the clips were removed and the wound was opened widely and irrigated and débrided. If the laceration of the skin was too small to permit adequate exposure for purposes of inspection, débridement, and irrigation, it was enlarged. Regardless of the degree of soiling, severed tendons and nerves in wounds treated within 8 hours of the time of

injury were sutured immediately. This can be done with little risk of infection if the wound has been properly prepared by copious irrigations and thorough débridement and by the topical application of sulfanilamide.

4. Prophylaxis. Tetanus antitoxin was administered routinely. Clostridium welchii and perfringens antitoxin was not used.

Routinely we gave all wounds immediately a course of x-ray therapy upon the assumption that these rays are as effective in preventing infection from Clostridium welchii and other gas forming anaerobes as they are in the treatment of established infections.

5. All wounds of the extremities were immobilized either in traction or by splinting or casting. If a cast had been applied a small window was immediately made to expose the wound for purposes of frequent direct inspection and palpation.

6. All patients with major wounds were hospitalized for at least 48 hours. During this period they were kept at complete bed rest with the injured part, if an extremity, elevated above heart level. This period of hospitalization was insisted upon to assure constant observation by trained observers. During this period a minimal fluid intake of 2,500 cubic centimeters was maintained by mouth or parenterally when the oral route was not available or adequate. Blood was given until relatively normal levels of hemoglobin and red cells had been attained. Vitamin B-complex and Vitamin C were given in therapeutic doses routinely.

This series consisted of 25 cases, 14 cases with compound fractures of the major long bones, 9 with major lacerations, and 2 with shotgun wounds received at close range. Not one patient in the entire group developed a primary infection or a subcutaneous suppurative process and in 13, or 50 per cent of the cases, the wounds healed *per primam*. Both shotgun wounds, one of the thigh and one of the flank, were left open because it was impossible to close them after the shreaded wound margins had been excised. In 8 of the 14 cases with compound fractures, and in 2 of the 9 with major lacerations, there was failure of primary healing of portions of the approximated skin edges. This we attributed to tension and to devitalization of the edges of the skin flaps as the result of the original trauma. In all but one of these cases retraction of the flaps left only superficial open surfaces which healed by granulation. One compound fracture of the tibia re-compounded when the skin flaps retracted. In only 1 case was the granulating surfaces sufficiently large to make the grafting of skin a feasible aid to more rapid epithelization. All fractures promptly united and in no case did osteomyelitis develop.

In allocating credit for the prevention of infection in these cases it is our impression that, as in the case of the experimental animals, the implanted sulfanilamide powder played a large part, but a part secondary to the thorough débridement and the profuse mechanical washing with saline. That sulfanilamide is a valuable adjunct is attested to by the reported clinical experiences of many observers among whom may be mentioned Jenson et al., Stuck et al., Key and Lembeck, Campbell and Smith, Hodgeson and McKee, Johnson and Davis, Colebrook, and Brown et al.

Although there is good evidence that it is safe to place unsterilized sulfanilamide powder in wounds we have used only sterilized powder. By a very simple method the powder can be sterilized in an autoclave and at the same time be kept dry. The powder is placed in a glass container with a narrow neck and around its mouth two sheets of waxed paper are tightly secured. Prepared in this way the powder remains unchanged and as such retains its adhesive quality for the tissues.

WAR WOUNDS

Logically, the principles of treatment outlined should be effective in fresh injuries inflicted in military combat. The application of these principles under circumstances of war presents obvious difficulties. The foremost difficulty would be the provision of an adequate supply of sterile normal salt solution for copious irrigation of wounds. It is probable that this need could be met even near the line of battle by means of large tanker trucks from which the solution could be piped directly to dressing stations. It is also probable that such tankers could be provided with means for sterilizing and replenishing the supply as used.

CONTAMINATED OPERATIVE WOUNDS

The same principles of copious saline lavage followed by implantation of sulfanilamide powder have been used by us in 31 contaminated or potentially contaminated operative wounds. These were principally abdominal wounds through which gangrenous or recently perforated appendices had been removed, appendiceal abscesses drained, perforated peptic ulcers closed, and gastric and intestinal surgery performed. In this series of 31 cases, suppuration developed in only 2 wounds, an incidence of 6.5 per cent. This is impressive when compared to a previous similar series of untreated wounds in which there was an incidence of 29.8 per cent. The same principles were applied to 17 large clean wounds, such as those of thorocoplasty, radical breast and ventral hernia, with the result that all healed without suppuration. Applied to abdominal wounds, the technique consisted first of water-tight closure of the peritoneum. All surfaces of the wound were then exposed by retraction while salt solution was poured repeatedly into the wound or washed over it with a large syringe. The wash solution was removed with an aspirator. The surfaces were then covered with a thin layer of sulfanilamide powder.

Very convincing evidence of the efficacy of this form of treatment was presented by 2 cases. Both had appendiceal abscesses which were explored and opened through right rectus muscle splitting incisions because there was some doubt before operation relative to the nature of these inflammatory masses. Drains were inserted through stab wounds in the oblique muscles. After tight closure of the peritoneum the original rectus incisions were copiously lavaged and powdered with sulfanilamide. With a second set of sterile drapes, gloves, and instruments, the wounds were closed in layers without drainage. They were dressed separately and thus isolated from the stab wounds. In both cases the wounds healed *per primam* while the stab wounds drained freely.

CONCLUSIONS

1. The application of bactericidal agents to contaminated wounds of rabbits did not prevent infection and suppuration. Furthermore, they caused moderate to severe tissue damage, and interfered with the repair of bone either by direct action or through failure to prevent infection.

2. Sulfanilamide was more effective than bactericidal agents in preventing suppuration of contaminated wounds. It caused no apparent tissue damage and did not interfere with the repair of bone.

3. From the experimental and clinical evidences presented it would appear that infection in contaminated fresh traumatic and operative wounds is most effectively prevented by copious mechanical washing with salt solution followed by débridement and the implantation of sulfanilamide powder.

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A STUDY OF THE MECHANICS OF BILE FLOW

I. Responses to Physiological Intravenous Solutions

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THE biliary stream from its beginning within the intrahepatic bile ducts to its terminus within the duodenum is subjected to a multitude of influences, some impeding and others enhancing the flow of bile. These, in the order of their occurrence, are: (1) secretory pressure of the liver; (2) contractility and storage function of the gall bladder; (3) the *collum cysticum* sphincter located within the neck of the gall bladder; (4) the valves of Heister within the cystic duct; (5) respiratory effects on intra-abdominal pressures; (6) resistance of a sphincteric mechanism within the intramural portion of the common bile duct (sphincter of Oddi); and (7) duodenal tonus and motility.

The factors which have most experimental proof and about which most controversy continues, include the activity of the gall bladder, the sphincter of Oddi, and the duodenum. It would appear important, therefore, to investigate simultaneously the physiological relationships of these 3 factors to each other and their responses to a variety of stimuli. To the authors' knowledge no complete graphic presentation of such information has come forth. We wish to report here the method and the simultaneous responses to these organs to the administration of intravenous solutions in common use. In subsequent papers we shall describe the effects of agents introduced into the duodenum, and of drugs and pharmacological preparations.

LITERATURE

There appears to be a paucity of muscle fibers in the wall of the gall bladder which accounts for the reluctance of many investigators to assign to the gall bladder the power of contraction and evacuation. In some measure this can be explained by the difference in microscopic sections taken from distended vesicles and those taken from vesicles which have recently evacuated following stimulation by a fat meal (3, 4). The muscle fibers about the neck of the gall bladder have been assumed to form a *collum-cysticum* sphincter but there is no evidence for its function under physiological conditions (18, 22, 25, 33).

Francis Glisson, in 1654, was the first to suggest the possibility of a sphincter at the opening of the bile duct into the duodenum, and in 1879 Simon Gage described its histology (13). Rugero Oddi was led to the discovery of its importance in 1887, after observing the dilatation of the extra hepatic bile ducts following cholecystectomy (32). Oddi's name has been affixed to this structure because of the volume of work done by him at that early date. Not only did he demonstrate its existence in a variety of mammals but he was the first to cannulate the peripheral end of the severed common duct and measure the resistance offered to the flow of fluids—a method again popular in the last decade. In the subsequent literature a controversy arose on the existence of an independent anatomical sphincter, but a majority of workers have been able to compile convincing evidence that a group of muscle fibers encircle the lowermost point of the common bile duct which could act as a special sphincter (4, 5, 14, 17, 24, 25, 30, 34).

The present concept of what is commonly called the "sphincter of Oddi" in reality consists of two parts: a long ampulla which is surrounded by a thick coat of obliquely arranged muscle fibers, the thickest coat found anywhere in the extrahepatic biliary system; and a small terminal ring in the tip of the papilla composed of circular muscle fibers. This latter structure alone is capable of opposing the flow of bile.

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A preliminary report was read at the Meetings of the American Physiological Society, April 19, 1941, Chicago.

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The entire extrahepatic biliary system has a dual nerve supply: parasympathetic fibers from the vagus nerve and sympathetic fibers from the splanchnic nerves. A controversy, which still remains unsettled, concerns which of the two carry motor and which inhibitory impulses. More recent work suggests that motor and inhibitory fibers may be found in the same nerve (23).

This discussion of the nervous supply of the extrahepatic biliary tract has considerable practical import, for from it evolved several therapeutic and diagnostic developments. Foster, in 1880, was the first to suggest a reciprocal innervation between gall bladder and sphincter of Oddi; i.e., when the gall bladder contracted, the sphincter relaxed. The reader is referred to the bibliography of Ivy for the extensive literature on this particular phase of the subject.

The maximal intragall-bladder pressure does not exceed the secretory pressure of the liver, thereby permitting a free flow of hepatic bile into the gall bladder which occurs during the fasting period, when the sphincter is closed. With the first meal containing a stimulus for gall-bladder contraction the sphincter relaxes and the intraductal pressure falls to a level against which the gall bladder can now easily contract and evacuate itself (9, 27) either by reflex or by the same factor which makes the sphincter open itself. The normal physiological stimulus for the evacuation of the gall bladder is the passage of gastric chyme, following ingestion of fat or protein, into the duodenum.

Whether the sphincteric action of the end of the common duct is due to a true and independent sphincter or is determined by duodenal activity alone, or is regulated by both, has provoked much debate. A great part of the difficulty can be ascribed to the problems inherent in attempting to separate the activity of two so closely approximated structures. That duodenal peristalsis plays a rôle in the flow of bile into the duodenum is a fact accepted by the majority of workers. However, many have found that bile sometimes may be discharged without regard to duodenal activity. We believe our method has clarified this situation in a graphic manner.

That the flow of bile is dependent upon changes in intra-abdominal pressure incident to respiration has been thoroughly disproved (8, 15, 17) despite the insistence of some (6, 7, 20, 35).

That a discussion of the physiology of the mechanism of bile flow bears considerable practical import can be illustrated best by the development in recent years of a relatively large literature on biliary "dyskinesia" or "dyssynergia." Interest in this subject was aroused when surgeons could not account for the obstruction to the biliary tract with the usual pathological findings. A physiological obstruction of the sphincter of Oddi was then proposed as a possible etiological factor. The reader is referred to extensive reviews of this interesting subject (2, 17, 29).

METHODS

The method in most common use today for determining the pressure within the common bile duct goes back to Oddi in 1887. He severed the common bile duct and inserted a cannula into it, directed toward the duodenum. The cannula was attached to a mercury column and the level of the column at which drops of mercury were seen to appear at the papilla of Vater was taken as the intraductal pressure. Oddi found it to be the equivalent of 675 millimeters of water. Archibald used this method in attempting to show that bile pancreatitis must be due to a spasm of the sphincter of Oddi, but was the first to use a water manometer. He found intraductal pressures of 180 to 330 millimeters of water, which rose to 800 millimeters on application of 3 per cent hydrochloric acid directly to the papilla. Mann (26), using this technique, has studied the sphincteric resistance in a great variety of species. Other methods of studying the sphincteric mechanism which have been used include visual observations of the exposed papilla of anesthetized animals, comparing the effects before and after section or cocainization, transplanting the proximal part of the choledochus above the ampulla, creating external duodenal biliary fistulas, and measuring the height at which a column of fluid ceases to perfuse through the common duct. Lueth (23) in Ivy's laboratory perfected a cannula

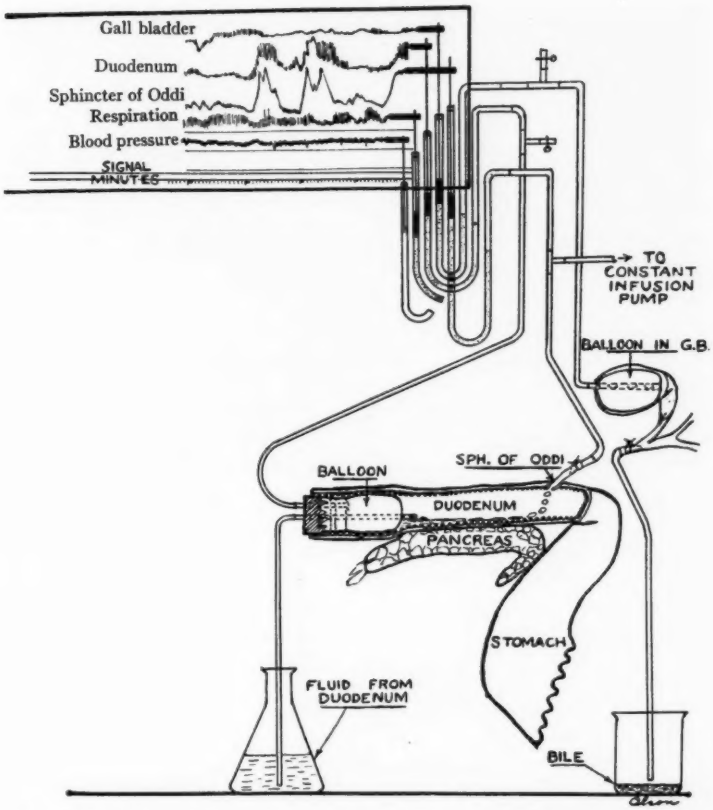

Fig. 1. Experimental procedure employed. Motility of gall bladder and duodenum recorded by balloon-oil manometer systems. Resistance of sphincter of Oddi to a constant perfusion with 0.9 per cent saline recorded by another oil manometer. Respiration recorded by balloon placed between the liver and diaphragm, leading to a fourth oil manometer. Blood pressure recorded by mercury manometer. Glass cannula projecting beyond duodenal balloon for drainage of perfusion fluid entering through the sphincter of Oddi and for injecting solutions into the duodenum.

with which the gradient of pressure within the common bile was determined. He also recorded simultaneously duodenal activity and the rate of drop perfusion through the sphincter. Konan, in Japan, used a technique similar to ours, but in his experiments, the rate of perfusion through the sphincter of Oddi does not seem to have been constant, his results were not recorded together, and he did not publish any of his records.

Our own experimental procedure is illustrated in the accompanying diagram (Fig. 1). Fourteen experiments were completed on normal healthy fasting dogs under light pentobarbital (nembutal) anesthesia (25 mgm. per kgm. body weight, intravenously). In 3 dogs supplementary ether anesthesia was required for maintenance; all of these 3 were female dogs. External heat was applied and parenteral solutions were administered, if necessary.

Condom balloons were inserted into the gall bladder and lowermost portion of the duodenum. The cystic duct was not ligated, to prevent vascular changes within the gall bladder, and in order not to destroy reflex

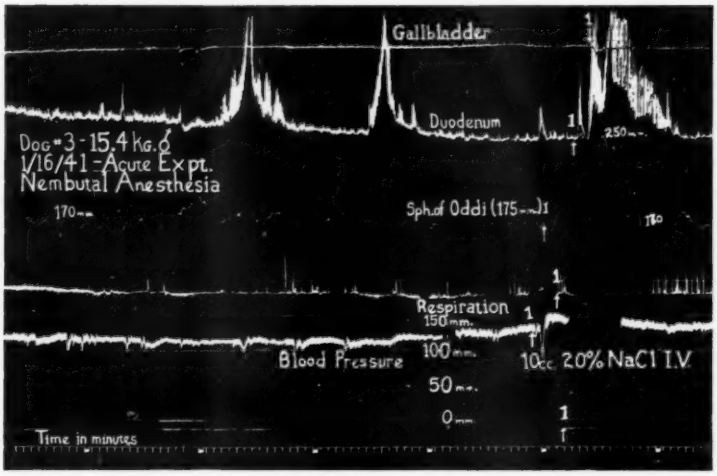

Fig. 2. A normal control period. There is little or no correlation between duodenal contractions and tone and resistance of the sphincter of Oddi. At *1* hypertonic saline given intravenously is seen to lower gall bladder tone and raise duodenal and sphincter tone simultaneously. (All records read from left to right).

pathways. Neither system was inflated with more than 15 cubic centimeters of air. The duodenal balloon was constructed over a glass cannula which projected beyond the balloon and provided drainage of the duodenal segment as well as a convenient method of intraduodenal instillation of solutions. Both of these balloons were attached to oil-carbon tetrachloride manometers (the specific gravity of the mixture was 1.5), which recorded the activity of the respective organs on a kymograph. The common bile duct was first cannulated proximally for the collection of bile, then the duct was severed, and the distal segment cannulated. The latter cannula was attached to a special manometer through which, by means of a T-tube device, a constant amount of saline could be perfused at a uniform rate, maintained by a constant injection pump—usually 2 cubic centimeters per minute—(28). Any resistance to the perfusing column of normal saline was immediately reflected by a rise of the manometer level. This proved to be a satisfactory method of measuring the sphincteric resistance because of the sensitivity of the manometer, because the portion of the duodenum containing the opening of the choledochus remained intact, and because, after preparation of the animal, the laparotomy incision could be closed for the remainder of the experiment. For recording respiration a large condom balloon was fixed between the diaphragm and the hepatic surface. This method of recording respiration was of advantage in that it permitted recognition of changes in the gall-bladder pressure referable to changes in intra-abdominal pressure.

Blood pressure was recorded by a mercury manometer, through a cannula in the common carotid artery; a solution containing 2 cubic centimeters of heparin (Connought) in 500 cubic centimeters normal saline was used to prevent clotting. The femoral vein was cannulated and prepared for the administration of intravenous solutions. The volume of bile secretion was recorded at intervals. All manometers recorded simultaneously on one paper, and all procedures were marked by a signal magnet.

The experiments were conducted as continuous observations on each dog as long as his condition remained satisfactory. It was not infrequent that individual experiments were carried on for periods of 12 or more hours each.

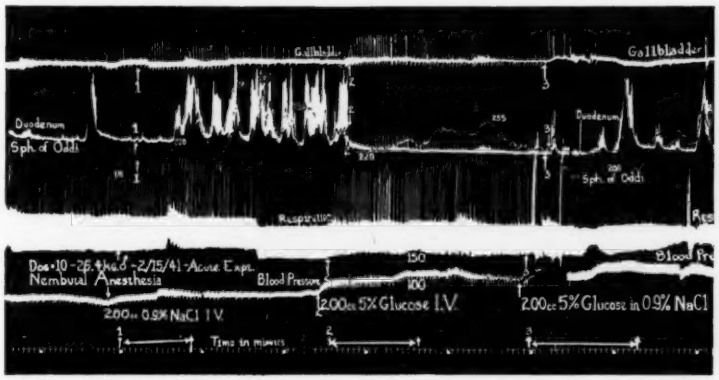

Fig. 3. At *1*, normal saline, given intravenously, produced 50 to 100 millimeter rises in sphincteric pressure with simultaneous increase in duodenal tone and motility. At *2*, 5 per cent glucose, intravenous, produced a marked depression of duodenal motility and tonus with a gradual rise in sphincteric resistance. At *3*, a combination of glucose and saline, intravenous, produced similar rises in sphincteric pressure as when saline alone was given, but the duodenal response was less than with saline alone. Gall-bladder tone and motility increased.

RESULTS

Normal activity. The sphincter of Oddi has a regular and distinct tonus rhythm. There are 10 to 20 millimeter changes in pressure which are manifested as rather large and irregular fluctuations on a control tracing. Superimposed upon these large fluctuations are 2 to 3 millimeter oscillations. We have not been able to discern three separate types of motility as described by Higgins and Mann. The sphincter tonus is completely independent of the tonus of the gall bladder, and there is a surprising lack of correlation between duodenal and sphincter activity. We have frequently noted subtetanic contractions of the duodenum to occur during normal control periods which were not associated with any significant changes in the intraductal pressures (Fig. 2). In some animals it is quite true that marked duodenal spasm was coincident with spasms of the sphincter, but even in these animals this was not invariably the rule.

The motility of the gall bladder is usually manifested as 3 to 5 millimeter changes in tonus occurring at a rhythmic rate; gall-bladder activity under normal conditions was found to be independent of the spontaneous activity of the duodenum or of the sphincter and vice versa. Marked respiratory effort producing deep excursions of the diaphragm could be immediately recognized in the gall-bladder tracing and were not confused with true alterations in gall-bladder activity. At no time was there a correlation between the state of tone of each of these three organs with blood pressure and respiratory changes.

Responses to physiological intravenous solutions. The administration of 200 cubic centimeters of normal saline intravenously was always followed by a significant increase in sphincter tone averaging about 100 millimeters. (18 experiments on 12 animals) usually associated with a marked increase in duodenal tone and motility (Fig. 3). There was no consistent change in gall-bladder motility due to normal saline and the blood pressure showed a consistent and prolonged elevation during the administration of the solution. The use of hypertonic saline, 10 to 20 cubic centimeters of 20 per cent sodium chloride intravenously, was followed by even more marked results in the direction produced by normal saline (Figs. 2 and 4). The gall bladder showed a consistent decrease in tonus in every 1 of the 20 instances in which hypertonic saline was used. These responses were more immediate and more marked than with normal saline, but less prolonged. The observations on the duodenum are in line with pre-

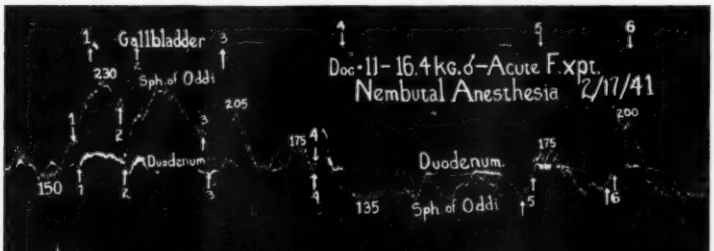

Fig. 4. The effects of drugs on spasm induced by hypertonic intravenous saline, *1*. At *2*, 0.3 milligram nitroglycerin, intravenous, produced a sharp transitory drop in sphincter pressure with a similar fall in duodenal tonus. At *3*, 4 units of padutin had similar but more prolonged effect on the sphincter without affecting duodenal activity, and in addition, produced gall-bladder contraction. At *4*, 20 milligrams trasentin produced a prolonged lowering of sphincter resistance 5 minutes after injection, and the following intravenous injections of hypertonic saline at *5*, or of gastric juice—intraduodenal—at *6*, which usually produced marked sphincter spasm were much less effective following the trasentin. Duodenal motility was practically abolished by trasentin.

vious work on the effect of normal and hypertonic solutions of saline on intestinal activity (16, 19, 31). The effects of normal saline on sphincter and duodenum were abolished by atropine in one instance and decreased by trasentin A in another. These agents have little influence on the spasm producing effect of hypertonic saline (Fig. 4). Nitroglycerine and padutin[1] produced temporary relaxation of sphincteric spasm induced by hypertonic sodium chloride (Fig. 4).

Intravenous injection of 200 cubic centimeters of 5 per cent dextrose in distilled water was given intravenously to 8 animals. Sphincter resistance increased in 3, was not influenced in 3, and decreased in 2. However, in practically every instance there was a marked decrease in duodenal tone and motility. It is interesting to note that a 30 to 50 millimeter increase in sphincteric resistance occurred in spite of the decrease in duodenal activity (Fig. 3).

The intravenous injection of a 5 per cent glucose solution after intraduodenal administration of magnesium sulfate and sodium sulfate was associated with a rise in sphincteric pressure but with a continued depression of duodenal activity. Twenty to 40 cubic centimeters of a hypertonic solution of dextrose was employed in 9 dogs with effects no more marked and less prolonged than with 5 per cent dextrose. Reports are contradictory relative to the effect of intravenous dextrose on intestinal peristalsis, but our results are in agreement with the work of Ochsner et al. (11, 12). The rise in blood pressure seen was frequently greater than with normal saline.

Intravenous injection of 200 cubic centimeters of 5 per cent dextrose in 0.9 per cent saline was employed in 8 dogs with unpredictable results somewhere intermediate between the effects produced by either solution alone. The combination of those two solutions produced greater rises in blood pressure than either alone (Fig. 3).

ANALYSIS OF STUDY

The graphic evidence of the independence in the activity of the sphincter of Oddi and the

[1] Vasodepressor urine extract of Kraut and Frey.

duodenum during a control period offers convincing proof in confirmation of the work of many. We have observed similar independent responses to drug stimulation. It must be clearly stated, however, that most frequently these two structures respond in an identical manner, if not at the same interval.

The effects of intravenous injection of normal saline solution on the duodeno-sphincteric mechanism was unexpected and challenging. In most experiments a prolonged and extensive rhythmic wave of contraction or spasm was produced in both the sphincter and duodenum. This is best demonstrated in Figure 1. The gall bladder did not usually react and atropine or trasentin abolished or diminished this effect of normal saline solution. This latter observation may be of importance in treatment of stones in common duct when intravenous saline has to be given.

Another physiological solution, namely 5 per cent glucose in distilled water did not affect the duodenum as did saline solution, but produced a moderate but prolonged contraction of the sphincter of Oddi, as demonstrated in Figure 3. The duodenum was relaxed following the injection of glucose.

Therefore a combination of both was tried, namely 5 per cent glucose in 0.9 per cent sodium chloride. This was followed by a slight contraction of the gall bladder, a primary depression of sphincteric and duodenal tone which would have permitted emptying of the gall bladder and which lasted for several minutes: following this, waves of contraction of the sphincter and of the duodenum occurred (Fig. 3). If these experiences can be applied to man, and they may be easily tried without harm to the patient, it may be a good procedure in cases of stones impacted in the common duct, and particularly in the ampulla.

Hypertonic solutions of sodium chloride in small amounts, administered intravenously, were consistently followed by great rises of sphincteric tone, as well as of duodenal tone and contractions (Figs. 2 and 4). The gall bladder showed a small and short relaxation. Again, this observation may be of importance if it can be applied to the human. Hypertonic saline has been recommended for treatment of paralytic ileus, but in case of impacted stone it may be contraindicated because a prolonged spasm of the duodenum and of the sphincter, together with the pressure of liver bile, may be disadvantageous in such conditions. Previous administration of a small dose of atropine or trasentin diminished this phenomenon somewhat both in power and duration, but did not abolish it.

The effects of normal and hypertonic saline solution on contractions of the sphincter and duodenum were so marked and so regular that it was possible to use this procedure for testing the effects of spasmolytic drugs on both structures.

SUMMARY

1. A method for simultaneously observing the activity of the factors most concerned with bile flow from the gall bladder has been described.

2. Sphincteric response can be independent of duodenal activity.

3. Normal or hypertonic saline administered intravenously induces prolonged periods of spastic contraction of the sphincter of Oddi and the duodenum which would constitute opposition to the flow of bile.

4. Glucose in distilled water, administered intravenously in isotonic or hypertonic concentrations, relaxes the duodenum and produces moderate contraction of the sphincter, which would offer little resistance to the flow of bile.

5. Glucose in normal saline, administered intravenously, produced an unpredictable effect, somewhat intermediate between the effect produced by either solution used alone.

6. The spasm producing effects of normal saline can be reduced or prevented by the use of atropine or trasentin intravenously, whereas these drugs are without significant effect on the spasms induced by hypertonic saline. Nitroglycerine, amyl nitrite, and padutin, given intravenously were effective in temporarily relieving the spasms produced by hypertonic saline.

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CLINICAL STUDIES ON THE ANTIHEMORRHAGIC EFFECTS OF A NEW WATER-SOLUBLE VITAMIN K-LIKE SUBSTANCE

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THE discovery and isolation of vitamin K and the synthesis of substances having vitamin K-like activity constitute not only a triumph of modern chemistry but also an important advance in therapeusis. Before the discovery, only a few years ago, by Dam (8–11) of the specific fat-soluble substance called vitamin K, surgeons feared the aftermath of operations in obstructive jaundice, as obstetricians and pediatricians did the latent and active hemorrhagic diseases of the newborn, and clinicians the hemorrhagic diathesis of the cholemic state.

Dam and his coworkers are rightly credited with the discovery of vitamin K and also with postulating its economy in the animal organism. He designated the substance as the "koagulations" vitamin or vitamin K. Dam was guided to the discovery of the substance through his work on cholesterol and its possible synthesis by the hen. He had previously observed that the use of his experimental diet was followed by hemorrhages as well as by an erosive ulceration of the gizzard. The observations of Dam were soon confirmed by other workers and the literature became materially enriched and a rational basis was established for the clinical use of the substance. Almquist and Stokstad (2) were among the early workers on the problem and, simultaneous with, but independent of Dam, established the existence of vitamin K as a substance needed by the chick to maintain normal clotting time of blood.

Once the existence of vitamin K was definitely established, workers turned their attention to its isolation and synthesis. Early in 1939, Dam and his coworkers announced the isolation of vitamin K in a relatively pure form. This announcement was closely followed by the publication of a report by Almquist and Klose (1) on the antihemorrhagic activity of synthetic 2-methyl-3-hydroxy-1, 4-naphthoquinone or phthiocol. They found that the physical and chemical properties of this compound simulated those known for vitamin K. In a letter to the editor of the *Journal of the American Chemical Society*, Binkley, MacCorquodale, Cheney, Thayer, McKee and Doisy (3) announced the preparation of the diacetates of dihydro vitamin K_1 and dihydro vitamin K_2 as further evidence that they had actually isolated both substances.

The syntheses of various quinones with vitamin K activity were announced in rapid succession. Among these was the tetra sodium salt of 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester which forms the basis for this report, and which for brevity will hereafter be referred to as preparation N-123. This substance was found by Foster, Lee and Solmssen (12) and by Almquist and Klose to possess on a molecular basis an activity much greater than that of methyl-naphthoquinone. It has been found in pharmacological studies that preparation N-123 has a wide margin of safety and adverse effects are absent in therapeutic doses.

The rationale of the clinical use of vitamin K and substances having vitamin K activity is the ability of such preparations to restore plasma prothrombin to normal levels. Vitamin K is absolutely essential for the coagulation of blood, and bile salts are necessary for the absorption of the substance from the intestinal tract. The clinical literature on the subject is rapidly expanding and published reports from various clinics are in agreement with our findings in the present study.

Butt, Snell and Osterberg (4, 5) found that the prolonged prothrombin time was reduced to within normal limits through the ad-

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TABLE I.—RESULTS WITH PREPARATION N-123–10 MILLIGRAM DAILY DOSE INTRAMUSCULARLY ADMINISTERED

No.	Patient	Diagnosis	Prothrombin level							
			Preliminary %	Medication period†					Post medication period	
				1st dose %	2nd dose %	3rd dose %	4th dose %	5th dose %	48 hrs.* %	72 hrs.* %
1	T. B.	Carcinoma of colon with colostomy	70	84	80	70	70	75	75	75
2	E. B.	Carcinoma of pancreas with liver metastasis	72	100	82	100	80	90	100	100
3	M. C.	Carcinoma of head of pancreas with jaundice	29	94	100	100	98	90		43
4	R. D.	Carcinoma of colon with metastasis to liver	69	65	73	100	90	90	73	70
5	A. Do.	Carcinoma of pancreas with diabetes	78	85	90	86	90	100	100	100
6	E. H.	Common duct stone	50	82	100	100	100	100	100	100
7	W. H.	Common duct stone and sepsis	68	72	76	79	100	100	100	100
8	C. J.	Acute cholecystitis with jaundice	78	64		88	75	99	100	100
9	H. M.	Obstructive jaundice	70	93	80	81	100	100	100	100
10	J. M.	Gastroenterostomy with secondary complications	89	90	100	100	100	100	100	100
11	N. P.	Liver abscess	80	90	100	100	100	100	80	80
12	J. P.	Obstructive jaundice with cirrhosis ‡	60	84	71	91	100	100	100	90
13	M. R.	Common duct stone and sepsis ‡	62	70	71	84	98	100	100	100
14	M. S.	Obstructive jaundice with slight biliary cirrhosis	61	69	72	64	100	90	100	100
16	A. T.	Carcinoma of pancreas, jaundice, urinary bladder infection	50	50	100	100	100	100	100	100
17	J. W.	Carcinoma of stomach and pyloric obstruction	70	80	70	90	100	100	73	75
19	F. W.	Catarrhal jaundice	78	80	66	90	75	100	100	100
18	C. W.	Empyema of gall bladder	75	80	76	90	100	100	100	100
20	D. T.	Intermittent obstructive jaundice with sepsis	48	100	100	57	57	70	100	100
35	O. B.	Cirrhosis of liver	55	90	100	100	100	100	70	65

*48 and 72 hours respectively, after last dose.
†Determination 24 hours after dose.
‡1st dose, 20 mgm., all other doses 10 mgm.

ministration of vitamin K and bile in their cases of obstructive jaundice. They observed that the administration of vitamin K concentrate with bile salts effectively prevented and controlled hemorrhagic diathesis, and that it made surgery in these patients less hazardous. Nygaard pointed out that transitory hypothrombinemia in the newborn may be prevented by the administration of vitamin K immediately after delivery. Scanlon and his coworkers tell of a case of obstructive jaundice in which postoperative bleeding occurred and which ceased following the administration of vitamin K. Smith and his coworkers reported that the use of vitamin K and bile salts effectively controlled postoperative bleeding in their cases. Butt, Snell and Osterberg (6) analyzed 63 cases studied at the Mayo clinic during a period of 2 years and demonstrated the value of the preoperative use of vitamin K. Eight of the 63 cases did not receive preoperative doses of vitamin K and 5 of these patients developed postoperative bleeding.

Stewart (22) holds that dangerous hemorrhage may occur when plasma prothrombin concentration is less than 50 per cent of normal. He states that a mixture of vitamin K and bile salts will restore plasma prothrombin and control the tendency to hemorrhage. Cheney established the safety of intramuscular administration in man. Stewart and Allen observed a marked reduction in plasma prothrombin in cases of obstructive jaundice with biliary fistulas. They found a mixture of vitamin K and bile salts to give prompt improvement. Patients who did not

TABLE II.—RESULTS WITH PREPARATION N-123–10 MILLIGRAM DAILY DOSE ORAL ADMINISTRATION

No.	Patient	Diagnosis	Prothrombin level							
			Preliminary %	Medication period†					Post medication period	
				1st dose %	2nd dose %	3rd dose %	4th dose %	5th dose %	48 hrs.* %	72 hrs.* %
21	M. P.	Common duct stone, gall bladder removed	77	80	75	100	100	100	100	100
22	H. R.	Common duct stone with jaundice	66	88	82	98	100	100	100	100
23	B. K.	Sepsis following gall bladder operation	30	58	76	65	80	51	50	50
24	S. J.	Subdiaphragmatic abscess	65	100	85	83	100	100	85	85
25	J. M.	Peptic ulcer with gastroenterostomy	69	85	100	100	100	100	100	100
26	S. N.	Carcinoma of stomach with metastasis causing common duct obstruction	43	100	100	100	100	100	100	100
27	T. N.	Vitamin deficiency, alcoholism, early cirrhosis	50	85	100	100	100	100	100	100
28	G. P.	Ruptured appendix	33	75	88	90	100	100	94	100
29	E. S.	Cirrhosis of liver	64	90	90	85	100	100	85	80
30	T. S.	Cirrhosis of liver (Banti's), hematemesis, enlarged spleen	75	90	100	100	100	100	80	80
31	E. B.	Carcinoma of head of pancreas	70	85	75	100	100	100	100	100
32	G. V.	Cirrhosis of liver with ascites	79	100	90	85	90	100	85	85
33	A. W.	Common duct stone	80	100	100	100	100	100	100	100
34	K. D.	Common duct stone and diabetes	50	73	83	90	100	100	100	100
36	J. N.	Carcinoma of stomach with metastasis to liver	25	75	100	90	75	85	100	100
37	J. S.	Cirrhosis of Liver	30	69	70	75	100	100	75	65
38	W. D.	Chronic cholecystitis	55	75	85	100	100	100	100	100
39	F. G.	Carcinoma of pancreas with liver metastases	60	100	70	75	75	100	100	100
40	E. H.	Cirrhosis of liver	68	70	75	100	90	80	80	80
41	M. K.	Pericholecystic abscess with jaundice	60	100	100	100	100	100	100	100

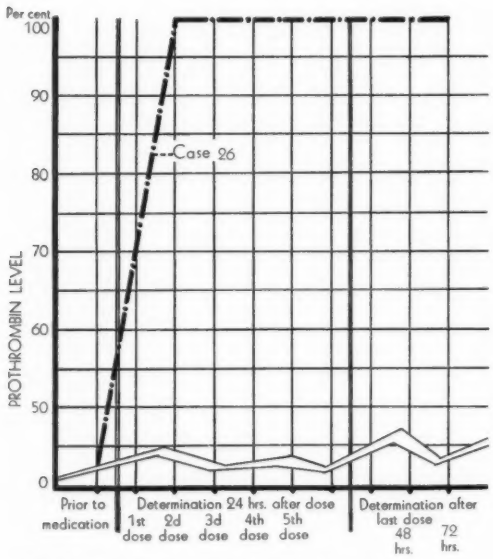
*48 and 72 hours after last dose.
†Determination 24 hours after dose was administered.

receive vitamin K before operation and who experienced severe postoperative bleeding were found without exception to have a plasma prothrombin concentration below 45 per cent. Olson and Menzel reported on the use of vitamin K in 24 cases of obstructive jaundice. They recommend the use of vitamin K and bile salts in all cases of jaundice, both before and after operation. Rhoads and Fliegelman used a synthetic vitamin K preparation for the treatment of prothrombin deficiency in 10 patients, 9 of whom responded satisfactorily to the therapy. Norcross and McFarland used a synthetic vitamin K preparation in 22 cases of hypoprothrombinemia. They found that the substance effectively controlled bleeding except in the face of severe liver damage. No toxic manifestations were observed.

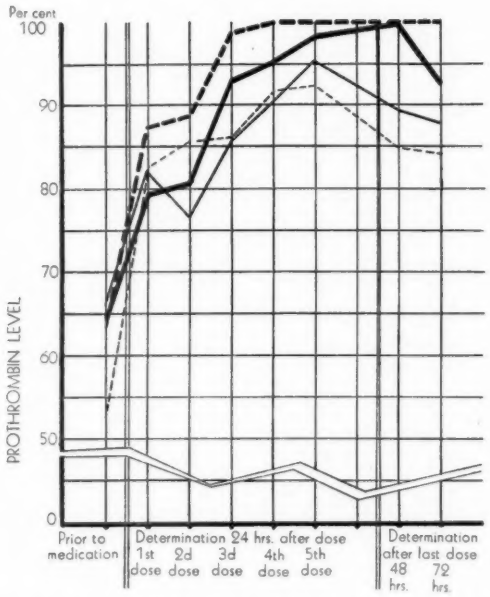
Kugelmass pointed out that severe cases of hemorrhagic disease in the newborn may be associated with prenatal transmission of the condition. This has been shown by the lowered prothrombin content of the blood of the expectant mother. He cited a number of such cases in which patients were successfully treated by the administration of vitamin K. Poncher and Kato had 22 cases of hemorrhagic disease of the newborn successfully treated with synthetic preparations of vitamin K; prompt cessation of bleeding occurred and in no instance were transfusions needed.

CLINICAL INVESTIGATION

This report summarizes our experiences with a vitamin K-like preparation, the tetra sodium salt of 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester or prepara-



Graph 1. Typical curve as obtained in patient with obstructive jaundice but without other complications.



Graph 2. Variations in prothrombin level curves of patients with and those without liver disease or sepsis. Patients without liver disease or sepsis: Oral administration – – – –, subcutaneous administration ———. Patients with liver disease or sepsis: Oral administration – – – –, subcutaneous administration ———.

tion N-123, in some 41 cases selected from the medical and surgical services of Cook County Hospital, Chicago. In most instances the patients represented cases of disease of the biliary tract or liver associated with jaundice. A small number of the cases studied had only gastro-intestinal disturbances or severe sepsis conducive to vitamin K deficiency.

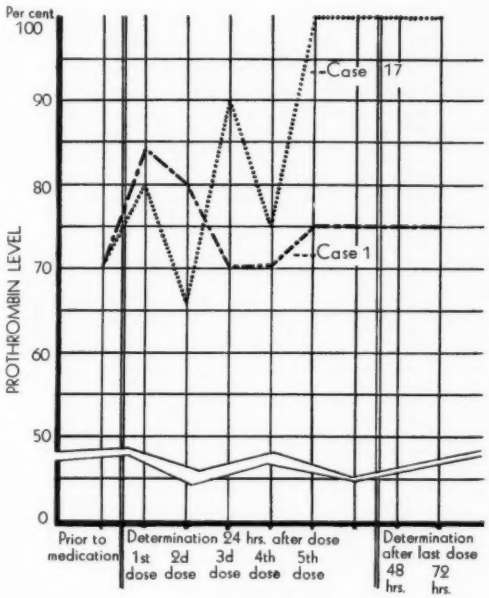
A preliminary determination of the blood prothrombin levels according to the modified Smith method (24) was done on each patient. Then a daily dose of 10 milligrams of preparation N-123 was given over a period of 6 days. The blood prothrombin levels were determined daily for 8 days. On the seventh and eighth days, the clotting time was also determined.

METHOD OF PLASMA PROTHROMBIN DETERMINATION

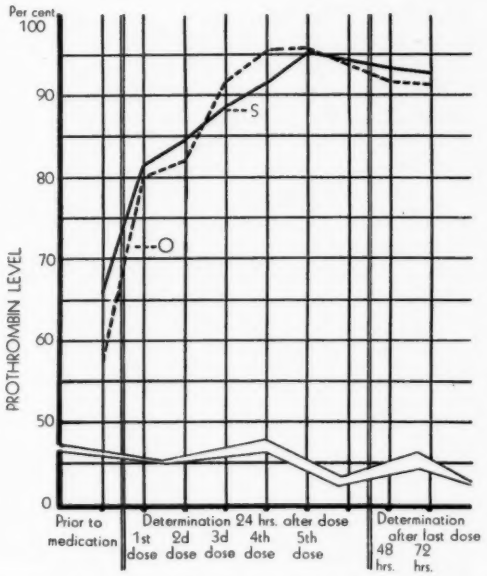
Rabbit brains and lungs are used as a source of thromboplastin. They are macerated in a mortar. Normal saline solution is then added and the material is placed in the ice box where it is permitted to stand for 3 hours. The supernatant fluid is decanted and strained through gauze. Usually the solution is centrifuged. The thromboplastin is kept in the ice box, and it is considered advisable to warm the sample of thromboplastin to room temperature be ore it is used. Because of the rapid deterioration in the activity of thromboplastin, a normal prothrombin time for the sample must be determined daily.

A stop watch is used to insure accuracy in obtaining the clotting time. One-tenth thromboplastin is placed in a serological tube. To this is added 0.7 cubic centimeter of blood, drawn quickly and automatically. The time is recorded in seconds from the time the blood contacts the thromboplastin until the time the clot appears in the tube. The tube is slowly inverted until clotting occurs. A normal individual is tested several times to obtain a correct normal clotting time against which patients are checked.

$$\frac{\text{Normal plasma prothrombin time in seconds}}{\text{Patient's plasma prothrombin time in seconds}} = \text{per cent of clotting activity.}$$



Graph 3. Bizarre prothrombin level curves obtained in patients with deficient food intake and deficient absorption (pyloric obstruction, colostomy).



Graph 4. Curves showing response in prothrombin level to oral, *O*, and subcutaneous, *S*, administration of preparation N-123.

A prolonged prothrombin time in seconds will give a low percentage of clotting activity. Levels below 70 per cent are to be considered dangerous, and hemorrhage may occur when such levels are reached.

Of the 41 patients in our series, 21 received a daily dose of 10 milligrams of preparation N-123, subcutaneously while 20 were given the substance per os. Of this latter group, 10 patients took the N-123 in combination with 5 grains of bile salts. The other patients did not receive any bile salts. In a small group of patients, blood prothrombin levels were determined hourly after injection of the initial 10 milligram dose. This was to determine just how rapidly the prothrombin levels rise after the patient receives the medication.

RESULTS WITH PREPARATION N-123

In most of our cases, the prothrombin level rose to normal limits within 24 to 48 hours after the initial dose of preparation N-123. After the 100 per cent level was reached and held by the daily dose, it could be maintained for 48 to 72 hours after the medication was discontinued. Exceptions to the foregoing occurred in a number of instances, for example when aggravation of an existing jaundice or other condition caused fluctuations (up and down) in the prothrombin level even during the period of medication. Lag or fluctuation in the response to the medication occurred also in cases with sudden appearance of high fever, profuse vomiting, or starvation. In the face of existing liver damage, a definite lag in the rise of the prothrombin level was observed, and in a few cases never reached 100 per cent; also prothrombin levels could not be maintained after medication was stopped.

Patients with pyloric obstruction, or after colostomy, or with severe sepsis and the attending starvation, present a response similar to that found in cases with liver damage. Infection plus liver damage was found markedly to retard response to the therapy. In one case the prothrombin level did not rise above 80 per cent. In a number of cases of jaundice complicated by sepsis, the prothrombin levels

reached normal only after about 96 hours. It is interesting to note that in some of these the prothrombin levels could be maintained for 48 hours after stopping the medication.

In our hands, cases of K-avitaminosis resulting from uncomplicated obstructive jaundice were found to respond promptly to preparation N-123, 10 milligrams daily, whether given parenterally or per os (Graph 1). In face of liver damage and resulting interference with vitamin K storage and utilization and in those cases with sepsis and gastrointestinal pathology (pyloric obstruction, colitis, etc.), in which absorption is also impaired, the response to the medication is less prompt, less complete and for a shorter period of time (Graphs 2 and 3). This observation is, of course, in agreement with that of other clinicians. Naturally the degree of hypoprothrombinemia, the condition of liver parenchyma, the state of the gastrointestinal tract and the absorption mechanism (when given per os), all play a rôle in the antihemorrhagic effect of any preparation possessing vitamin K-like activity.

It has been our observation that when the functional integrity of the liver is not greatly disturbed, impairment of vitamin K absorption as seen in certain gastrointestinal conditions and in sepsis is followed by hypoprothrombinemia only after a prolonged period of such impairment. A nearly normal prothrombin level was found in several instances of colitis, complicated peptic ulcer, etc., where K-avitaminosis was suspected because of small intake of food for a long period. However, in cases with liver parenchyma damage, a markedly decreased prothrombin level is nearly always present. Lowest prothrombin levels are found in cases of sepsis with liver damage and sepsis with obstructive jaundice.

SUMMARY AND CONCLUSIONS

The 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester tetra sodium salt, referred to as preparation N-123, a synthetic substance having vitamin K-like activity, was used in 41 cases. Satisfactory results attended its administration. The substance has been found to be more active, on a molecular basis, than methyl-naphthoquinone.

A daily dose of 10 milligrams, parenterally or per os, was found capable of raising prothrombin levels to normal within 24 to 48 hours. In many instances the normal level can be maintained for 24 to 72 hours after the medication has been stopped.

As is generally true of vitamin K preparations, the effectiveness of the substance is partially diminished in the face of liver parenchyma damage, gastrointestinal disturbances, or sepsis. The presence of any two of these factors calls for continuous administration of the preparation to maintain the prothrombin level.

Despite the fact that our patients were mostly far advanced and complicated cases, the results obtained by the use of preparation N-123 were quite satisfactory (Graph 4), even though the curves do not show such steep rise as seen in the uncomplicated cases (Graph 1).

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BACTERIEMIC STAPHYLOCOCCAL INFECTION

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CULTIVATION of bacteria from the blood was first used for the study of infections due to anthrax bacilli, plague bacilli, and hemolytic streptococci. As a result of this early experience with highly invasive bacteria a positive blood culture report has been accorded undue clinical significance with connotations as to bacterial virulence and absence of host resistance. The demonstration of viable bacteria in the circulating blood is important only in relation to the kind of bacteria found and the pathological anatomy of the lesion which permitted the breaking down of the normal barrier to blood stream contamination.

A *sustained bacteriemia*, often referred to by the vague term of "septicemia," is characterized by the isolation of invasive bacteria of high virulence in relatively constant numbers per cubic centimeter of blood, a nonsuppurative cellulitis at the portal of entry and evidence of lymphatic transmission of the infection. Distinct from such blood stream infection is blood stream contamination by the *intermittent bacteriemia* of septic phlebitis or endocarditis which is characterized by a variable number of bacteria per cubic centimeter of blood, a peripheral or visceral focus of localized infection and complete absence of signs of lymphangitis. The organisms responsible for this latter type of bacteriemia need not possess any great invasive ability.

The importance of thrombophlebitis in the production of metastatic abscesses was recognized by John Hunter. Purulent phlebitis of major veins is an accepted complication of otitic and puerperal infections but septic thrombophlebitis of minor venous radicles as a cause of bacteriemia has received infrequent pathological (36) and clinical (16, 22, 32, 33, 37) consideration. In such papers it is made evident but not emphasized that the staphylococcus is the etiological organism found most frequently in bacteriemias arising from septic thrombophlebitis of minor venous radicles.

Academic researches upon staphylococcal infection have been more definitive. The staphylococci are of limited invasiveness and cannot maintain a phase in which the organisms are resistant to phagocytosis (19). The staphylococcal exotoxins are more poisonous for animals (5, 6, 7) than for human beings (34, 35, 39, 40). Further, toxigenicity is not a criterion of invasiveness as may be recalled by tetanus and diphtheria. The tissue response to staphylococcal infection is associated with prompt lymphatic obstruction and subsequent thrombosis of the vascular capillaries (24–31). This sort of evidence has led Topley to conclude that in a bacteriemic staphylococcal infection "the cocci are carried from the original focus of infection in detached fragments of an infected thrombus."

Final acceptance of this verdict would seem to depend upon its confirmation in clinical observations. The constancy of a suppurative focus in staphylococcal bacteriemia is a surgical axiom. Occasionally the bacteriemia complicates a peripheral lesion such as a boil or a carbuncle. More frequently the local focus is in the bone, brain, kidney, or endocardium, and there is no demonstrable portal of entry. Thus there is good ground for believing that an initial bacteriemia arising from a peripheral lesion is frequently asymptomatic but permits the implantation of bacteria in vulnerable organs. The staphylococcemic phase associated with visceral abscesses must necessarily be a recurrent bacteriemia related to the active visceral focus and independent of the healed or forgotten peripheral lesion. Figures 1 to 5 present evidence of the occurrence of septic thrombophlebitis in minor vascular radicles of various viscera from patients with bacteriemic staphyloccal infection.

During the past 15 years the Massachusetts General Hospital has collected complete autopsy records upon 33 patients in whom staphylococcal bacteriemia was the primary

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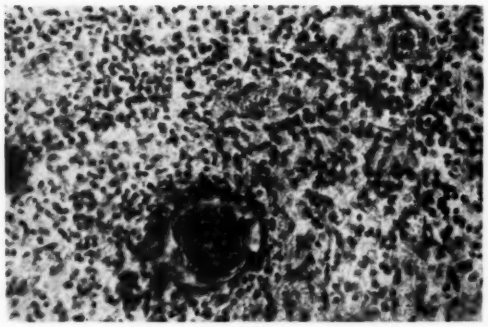

Fig. 1. Pathology No. 32–794 A. Septic thrombophlebitis in the metaphyseal focus of osteomyelitis.

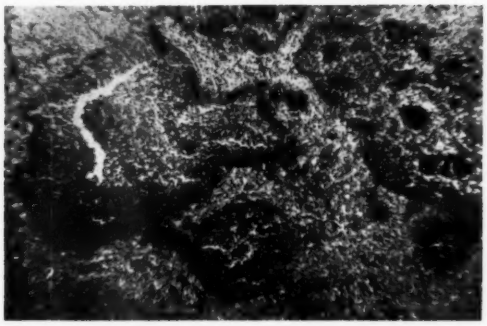

Fig. 2. Pathology No. 7010. Kidney abscesses with a blood vessel occluded by septic thrombus.

cause of death. The material has been analyzed in Table I. The first group contains the instances of suppurative phlebitis of major venous pathways. Deaths occurred as the result of direct extension of the thrombus to vital venous channels or as the result of massive pulmonary infarction. It is noteworthy that multiple visceral abscesses did not occur and that the lesions were confined to the involved veins and the lungs. The second group contains the instances of endocarditis. The classical pattern of peripheral and visceral infarction occurred with left endocarditis. Deaths from right endocarditis were attributable to the massive pulmonary infarction necessarily incident to such a lesion. The third group had in common one or more foci of abscess formation in the lungs and a pattern of peripheral and visceral infarction and suppuration which was entirely comparable to that seen as a result of left endocarditis. Death was not attributable to the lung lesions but rather to the peripheral and visceral metastases propagated from the pulmonary thrombophlebitis incident to suppuration of the septic lung infarcts. Myocardial abscesses occurred predominantly in this group. There were 2 cases with true petechiae and 4 instances of sterile visceral infarction. The fourth and last group of patients includes those with brain abscess and requires no discussion as to cause of death. It does not appear necessary to presuppose a retrograde contamination of the vertebral venous plexus from the caval system (2) to explain these abscesses.

Table II records the incidence of septic metastases to vital organs. Abscesses of the myocardium deserve special comment. Abscesses of the subendocardial portion of the myocardium may be followed by septic mural thrombi whereas abscesses of the myocardial periphery may be followed by pericarditis. Rupture of the heart through such an abscess is a recognized complication of the drainage of a staphylococcal pericarditis.

Table III summarizes the presumptive portals of entry in the reported cases. Abscesses or carbuncles, sinusitis, and prostatic infection were the chief known initial lesions. The incidence of prostatic infections is a reflection of the vulnerability to thrombophlebitis of the prostatic venous plexus. In the diagnosis of primary staphylococcal pneumonia it is important to remember that a septic pulmonary infarct may simulate pneumonia and still be the first clinical symptom of a visceral abscess.

The importance of pulmonary thrombophlebitis in staphylococcal bacteriemia is emphasized in the following case report:

An adolescent girl (Case No. 228574, 17 years of age) entered with an acute osteomyelitis of the upper end of the tibia and a sustained temperature of 105 degrees F. by rectum. Incision and drainage of the subperiosteal abscess was followed by intensification of her symptoms, pain in the chest, and a pleural friction rub. A femoral vein ligation was performed in the hope of preventing further pulmonary infarction. Coincidental cultures of blood from the femoral and antecubital veins failed to show conclusive evidence of a more intense contamination of the blood from the osteomyelitic focus.

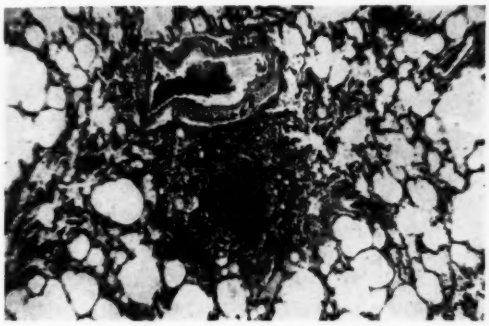

Fig. 3. Pathology No. 6208. Septic thrombophlebitis in the lung.

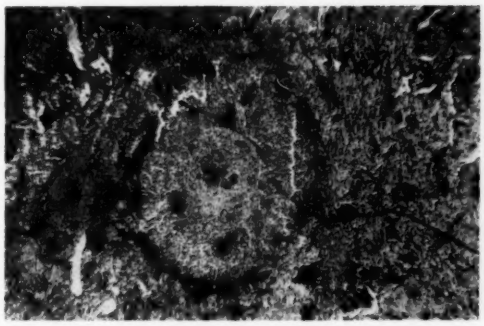

Fig. 4. Pathology No. 7010. Beginning organization of a septic thrombosis of a vessel in the lung.

There were no demonstrable emboli in the smear of the femoral blood. As is shown in Table IV there was a prompt reduction in the number of colonies of staphylococci in the peripheral blood after ligation of the femoral vein, and this was correlated with clinical improvement and a reduction of temperature. Four days after ligation of the femoral vein the temperature rose again, the patient became more severely ill and an intensification of the bacteriemia was noted. This was correlated with a more definite friction rub, râles, purulent sputum containing staphylococci, and an increase in the respiratory rate to 40 per minute. Portable x-ray films were not completely satisfactory but failed to show a recognizable abnormality. The intensity of the bacteriemia gradually diminished as the pulmonary signs and symptoms subsided. Urine cultures were consistently negative for staphylococci. The subsequent convalescence was uneventful except for a sequestrectomy, and the patient has failed to show any new foci during the 10 months since discharge. In retrospect it is felt that this patient entered with a bacteriemia incident to her osteomyelitis. This was arrested by femoral vein ligation after septic lung infarcts had occurred. A recurrent bacteriemia was associated with suppuration of the pulmonary infarcts as evidenced by pus in the sputum. It is important that these lung abscesses healed spontaneously.

Examination of this material has convinced me that staphylococcemia is dependent upon an intravascular focus of infection. It follows that every effort should be made in the management of staphylococcal abscesses to define the diagnostic features of septic thrombophlebitis in the stage before significant metastasis occurs. It is my clinical impression that a total white blood cell count of 15,000 or over is strongly suggestive of intravascular sepsis. Positive evidence of septic thrombophlebitis is given by a chill, a sudden spike of fever to 103 degrees F. or more, a pulmonary infarct, a positive blood culture, or a palpably thrombosed vein. Septic pulmonary infarcts may simulate pneumonic consolidation so closely that it is a common clinical error to label such lesions as "bacteriemic staphylococcal pneumonia." Such "pneumonias" are often the first clinical symptom of a peripheral visceral abscess, particularly vertebral osteomyelitis, or right sided endocarditis. This latter diagnosis has been made clinically by the demonstration of multiple pulmonary infarcts in bacteriemic patients with no demonstrable peripheral or visceral focus of infection.

Scott (37) has expressed the opinion that the surgical drainage of pus under pressure is the procedure of choice in treatment of the infected vascular bed. This is sound doctrine

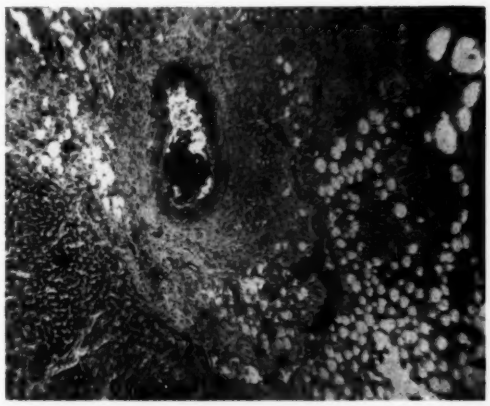

Fig. 5. Pathology No. 6007. Septic thrombus in a vessel in the heart.

TABLE I.—DEATHS FROM STAPHYLOCOCCAL BACTERIEMIA

	No. deaths	Total no. deaths
I. Thrombophlebitis and phlebothrombosis of major venous pathways		
a. Deaths due to extension to intracranial venous sinuses	5	
b. Death due to caval extension	1	
c. Deaths due to massive septic infarction of the lungs	2	8
II. Endocarditis		
a. Patients with left endocarditis, only one of whom showed a proximal pulmonary abscess	6	
b. Patients with right endocarditis	3	
c. Patients with bilateral endocarditis	2	11
III. Septic lung infarcts not secondary to endocarditis		
a. Patients with frank pulmonary abscesses and multiple peripheral visceral abscesses. Two of these 10 patients showed petechiae	10	
b. Patient with bronchopneumonia and myocardial abscess	1	
c. Patient with prostatic plexus thrombophlebitis, lung infarct and myocardial abscess	1	12
IV. Brain abscess		
a. Patient entered with a carbuncle of the neck and died of brain abscess and meningitis	1	
b. Patient entered with brain abscess and showed subsequent septic infarcts of lung	1	2
Total		33

but does not always prove effective. Persistent leucocytosis, fever, chills, or positive blood cultures have occasionally led me to excise the inflammatory focus with subsequent prompt control of the infection.

Neuhof (32, 33) and Meleney (22, 23) are advocates of ligation or excision of veins to control purulent phlebitis in a surgically accessible vein. Obviously this method cannot be applied to intracranial venous sinuses or pulmonary veins.

TABLE II.—INCIDENCE OF SEPTIC METASTASES IN VITAL ORGANS DISCOVERED AT AUTOPSY

Location	No. cases
Lung	28
Myocardium	11
Kidney	21
Brain and spinal cord	11

The intravenous injection of immune sera has appealed to many clinicians. Blair has recently completely reviewed the problem of staphylococcal pathogenicity and immunity. On the basis of factual experimental data uncomplicated by clinical impressionism it would appear that "within a definitely circumscribed area the injurious action of the cocci and their products may be intense" and "this capacity far outweighs any ability to produce toxin." Antitoxic immunity may prolong life in animals susceptible to the toxin but such immunity does not afford complete protection to infection. The existence of an antibacterial immunity has never been proved and I have been unable to correlate the presence of agglutinins with eventual recovery (Table V) although Valentine and Butler (40) thought that blood stream clearance of bacteria occurred more rapidly in the presence of such agglutinins. Undoubtedly many staphylococci are destroyed in patients that survive a staphylococcal bacteriemia. The nonspecific bactericidal ability of cells in the lungs, liver, and spleen should not be forgotten as a part of the normal clearance mechanism.

Table VI summarizes the mortality statistics for untreated and variously treated staphylococcemic infections. Such data are almost worthless because they are based upon the entirely false assumption that staphylococcal bacteriemia is a disease entity within itself. A reduction of the mortality rate from 75 per cent to 30 per cent may be statistically significant but it is far from the ideal mortality rate that might be anticipated with a specific antibacterial agent. It is significant that the intravenous injection of any of several foreign chemical substances appears to be effective in lowering the mortality rate. Meleney's (22) bacteriophage is prepared in a yeast extract broth, and yeast nucleic acid is known to increase the nonspecific resistance to staphylococcal infection (3, 13). The bur-

TABLE III.—PORTALS OF ENTRY

Primary infection	No. cases
Abscess	6
Carbuncle	4
Sinusitis	4
Pneumonia	2
Prostatic abscess or postoperative infection	4
Unknown	13

TABLE IV.—BACTERIOLOGICAL STUDY OF THE BACTERIEMIC PHASE IN A FEMALE

Clinical notes	Date	Source of culture	Time	Colonies per c.cm. blood		
				0.5 c.cm.	1 c.cm.	2 c.cm.
	Dec. 26	Antecubital vein	a.m.		20	
Incision and drainage subperiosteal abscess	Dec. 27					
	Dec. 28	Antecubital vein	a.m.		132	
Ligation of femoral vein	Dec. 29	Antecubital vein	12:30 p.m.	16	25 and 28	31
		Femoral vein	12:30 p.m.	10	28 and 40	62
		Antecubital vein	3:00 p.m.	11	7	12
		Antecubital vein	5:00 p.m.	4	2	7
	Dec. 30	Antecubital vein	10:00 a.m.	0	2	1
	Dec. 31				Positive culture only from 5 c.cm. of blood	
	Jan. 1					
Increase of pulmonary symptoms	Jan. 2	Antecubital vein	a.m.	9	14	38
	Jan. 3	Antecubital vein	a.m.	4	5	7
	Jan. 4	Antecubital vein	a.m.	1	1	1
	Jan. 8	Antecubital vein	a.m.	0	1	1
Convalescent	Jan. 10	Antecubital vein	a.m.		Sterile	

den of proof is quite clearly upon Meleney to exclude this nonspecific factor in view of the overwhelmingly adverse evidence afforded by animal experiments on bacteriophage therapy.

The importance of a nonspecific enhancement of resistance to staphylococcal infection is well illustrated by the experiments of Cowan in which active immunization with staphylococci or with a totally unrelated organism, Pasteurella pseudotuberculosis, was equally effective in increasing the survival rate of experimentally infected rabbits. The mechanism whereby nonspecific shock reactions increase resistance to staphylococcal infection is unknown and has never been shown to be due to a specific immune body. Peptone shock in dogs is followed by a prolongation of the clotting time of the blood which has been correlated with an increased heparin content of the plasma and a disappearance of the metachromatic granular material of the Ehrlich

TABLE V.—RELATIONSHIP BETWEEN PRESENCE OF AGGLUTININS AND OUTCOME

Probable focus	Agglutinins*	Antitoxin†	Result
Furuncle of hand	++++	Yes	Died
Carbuncle of face	++++	Yes	Died
Endocarditis	++	Yes	Died
Osteomyelitis	++	No	Died
Phlegmon abdominal wall	0	Yes	Died
Osteomyelitis	0	No	Survived
Osteomyelitis	0	No	Survived

*Antibacterial antibody as developed by patient and determined by slide agglutination (19).
†Commercial antitoxin 100,000 units injected intravenously.

TABLE VI.—MORTALITY STATISTICS IN STAPHYLOCOCCAL BACTERIEMIA

	Total	Survived	Died	Per cent died
With surgical drainage and transfusions				
Joyner and Smith (14)	16	8	8	50
Baker and Shands (1)	30	9	21	70
Longacre, Zaytzeff-Jern, and Meleney (18)	54	10	44	81
	100	27	73	73
With antitoxin				
Joyner and Smith (14)	13	11	2	15
Dolman (10)	64	29	35	55
Baker and Shands (1)	35	26	9	26
	112	66	46	41
With bacteriophage				
Lawson (17)	38	7	31	82
Scott (37)	8	4	4	50
MacNeal and Frisbee (21)	15	7	8	53
MacNeal and Frisbee (21)	100	25	75	75
Dutton (12)	7	6	1	14
Meleney (before 1936) (22)	15	4	11	73
Meleney (1936–1938) (22)	21	15	6	29
	204	68	136	70
With antibacterial serum				
Cadham (8)	10	9	1	10
Julianelle (15)	17	7	10	59
	27	16	11	41

mast cells of the liver (41). Such an autoheparinization might prove beneficial to a patient with bacteriemia arising from a septic thrombophlebitis. The successful treatment of 2 cases of bacteriemic staphylococcal thrombophlebitis of the cavernous sinus has been attributed to a combination of chemotherapy and heparin (20).

ANALYSIS OF STUDY

Bacteriemic staphylococcal infection has been analyzed from clinical and autopsy material. The weight of evidence favors the hypothesis first emphasized by Adams, Welch, and Virchow that the bacteriemia arises from an intravascular focus of infection. Such foci may occur as purulent phlebitis of major veins, as septic thrombophlebitis of minor venous radicles in and around a localized suppurative lesion, or as primary endocarditis. Septic pulmonary infarction with subsequent abscess formation is followed by peripheral infarctions which make it appear that septic pulmonary thrombophlebitis may be comparable to left endocarditis.

Such a conception of the source and pattern of staphylococcemia has a broad implication for successful therapy. Intravascular extension of a staphylococcal infection should be suspected in the presence of a leucocytosis of 15,000 or more, a chill, a sudden spike of fever to 103 degrees F. or over, a pulmonary infarct, a palpably thrombosed vein, or a positive blood culture. A direct attack upon the inflammatory focus may be made by excision of inflammatory foci, drainage of pus or venous ligation. The recognition of the bacteriemia as a complication of a localized inflammatory process makes it unlikely that immune serum or bacteriophage can at the present time supplant surgical treatment. The clinical results of treatment with antitoxin, antibacterial antibody, and bacteriophage do not suggest that such therapy is specific and it is entirely possible that such success as has been reported may be due to a nonspecific enhancement of resistance.

CONCLUSIONS

1. Staphylococcemia has been presented as arising from intravascular foci of infection.

2. Pulmonary thrombophlebitis has been considered as a factor in the perpetuation of a staphylococcal bacteriemia.

3. Metastatic abscesses follow a pattern consistent with septic infarctions.

4. Varied surgical management is important in the treatment of bacteriemic infection.

5. It is not clear that antibacterial serum, antitoxin, or bacteriophage have made a specific antibacterial effect in treatment of staphylococcemia.

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CARCINOMA OF THE ESOPHAGUS

Torek's Operation, Recovery

OSCAR IVANISSEVICH, M.D., and ROBERTO C. FERRARI, M.D., Buenos Aires, Argentina

ENCOURAGED by the enthusiastic and effective work of surgeons of the United States — Franz Torek, Willy Meyer, Lilienthal, Eggers, Hedblom, Garlock, Adams, King, Marshall, Ochsner, DeBakey, Churchill, Alexander, Scott, Ogilvie, Whipple, and Cartell—we faced the problem of the surgical treatment of carcinoma of the esophagus, and, although we failed in our first ten attempts, we finally succeeded in working out the technique described here.

Doubtless a decisive factor in the success of this technique described is the previous pneumothorax operation as originated by Arce. This technique has been employed by him and by us since 1919. It makes intrathoracic maneuvers easier not only for the operator but for the patient. We have had a large experience with this operation, especially in the treatment of tumors of the lungs and of the thoracic wall.[1]

[1]Ivanissevich, Egües y Fernandez J. C., Tecnica precisa para extirpar los tumores parietales del torax emergentes en la cavidad pleural. Bol. y trab. Soc. de cirug. de Buenos Aires, 1938, 22: 925. Bol. inst. de clin. quir., 1939, 123: 5. Rev. Asoc. méd. argent., 1939, 52: 404.

Fig. 1. Roentgenogram showing defect at the level of the middle third of the esophagus.

In our patient, we used spinal anesthesia with metycaine. We believe that spinal and general anesthesia with cyclopropane are usually recommended for this operation.

R. G., 87,887 of the Instituto de Clínica Quirúrgica, chair of professor Arce, M.D.

Lorenzo Tarpin, aged 52 years, laborer, Argentinian, who lived in General Pico F.C.S., province of Buenos Aires, came to the institute on September 27, 1940. His illness had begun 2 months previously with manifestations of mechanical dysphagia, noticeable at first in efforts to swallow solid foods. The first symptom he noticed was the detention of a bit of meat in the upper part of the esophagus. Twenty-four hours later the bit of macerated meat was expelled by the mouth. The sensation of a foreign body then disappeared and the passage of food was partially re-established.

This episode was repeated several times, however. The arrest of the nutritious bolus in the esophagus produced pain of moderate intensity, which disappeared once the

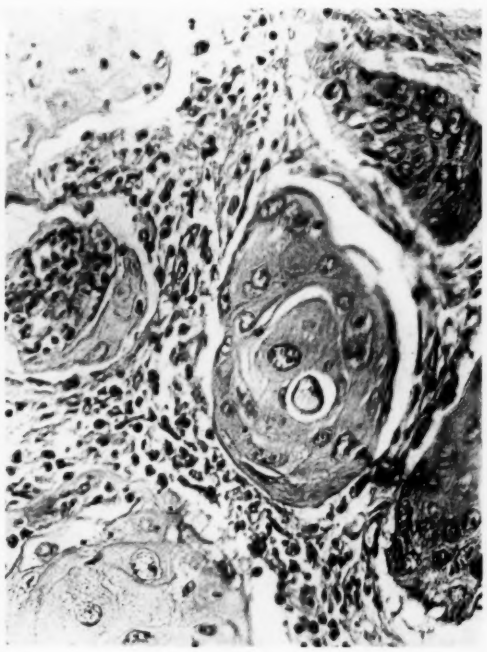

Fig. 2. Photomicrograph showing basocellular epithelioma.

Fig. 3. Left posterolateral thoracotomy.

Fig. 4. Wide costal resection.

food was expelled. Liquids could be swallowed normally. The swallowing of solids became more and more difficult, and the patient's general condition grew considerably worse. He lost more than 50 pounds in weight in 2 months.

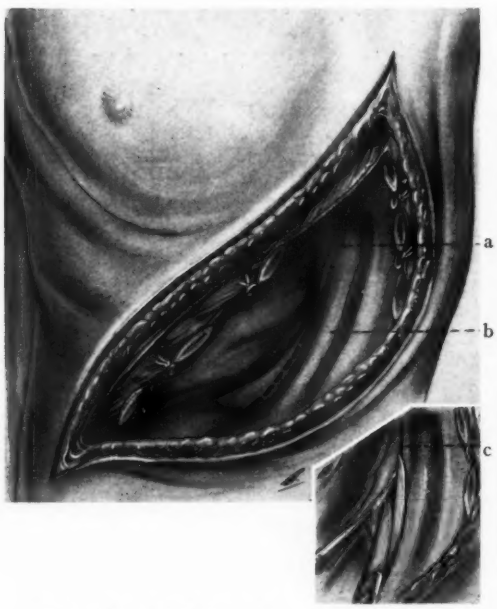

Fig. 5. After the soft parts between the ribs have been removed, the parietal pleura is opened. The dotted line shows the section of the pleura that covers the esophagus, a, line of incision; b, esophagus; c, incising pleura.

His family and personal history was without importance. He was not an alcoholic and smoked in moderation.

The clinical examination showed no ostensible evidence of illness. He was a tall man, well proportioned, of long lines, and had become much thinner. The muscular masses were moderately well developed. The teeth were in very bad condition both as to hygiene and conservation. There were no cervical glands. The respiratory and circulatory apparatus were in normal condition. The abdomen was normal. The roentgenographic examination, carried out when he entered the hospital, showed a characteristic image of incomplete stricture at the level of the middle third of the esophagus (Fig. 1).

On September 28, 1940, we performed an esophagostomy, which revealed at 37 centimeters from the dental arch an obstruction which consisted of a fleshy mass and which filled two thirds of the lumen of the organ. Examination of tissue removed showed a basocellular epithelioma (Dr. Niño, September 30, 1940) (Fig. 2).

The blood analysis showed red blood cells, 5,230,000; white blood cells, 8,400; hemoglobin, 16.43 grams (95 per cent); globular value, 0.91; volumetric index, 1.0; saturation index, 1.05; anisocytosis, slightly marked. Wassermann reaction was negative; Kahn reaction, negative. Coagulation time was 14 minutes; bleeding time, 1 hour and 25 minutes. Polymorphonuclear neutrophils numbered 67 per cent; polymorphonuclear eosinophils, 1 per cent; lymphocytes, 25 per cent; monocytes, 7 per cent (Dr. Niño, September 25, 1940). Chemical blood analysis revealed urea, 0.30; glucose, 1 gram per 1,000.

October 1, 1940, Professor Arce performed a gastrostomy following his own technique.

October 7, we performed the first stage of a pneumothorax (Arce). Three hundred cubic centimeters of air was introduced in the left pleura; the patient withstood the operation perfectly. October 12, the second stage of the pneumothorax with 400 cubic centimeters was performed, and on October 21, the third stage, when 700 cubic centimeters of air was introduced. Patient tolerated operation perfectly. The roentgenogram showed total collapse of the left lung. There was no subjective or objective manifestation indicating the functional annulation of the lung.

Fig. 6. Mobilization of the infra-aortic esophagus, marked by dotted line.

Fig. 7. Freeing esophagus from aorta and from bronchus at level of which the tumor was located by digital dissection.

On October 31, 1940, with the assistance of Drs. Ferrari and Lentino, I removed the carcinoma of the esophagus following our modification of Torek's technique. Goyenechea administered spinal anesthesia with 20 centigrams of metycaine, the patient being in supine lateral left position. Anesthesia was perfect throughout the entire thoracic stage of the operative procedure.

TECHNIQUE

An incision is made the whole length of the seventh rib and is extended behind and above, following the interscapulovertebral space. The

Fig. 8. Division and ligation of the esophagus, above, and, inset, invagination of the inferior stump beneath the pursestring suture made on the fundus of the stomach.

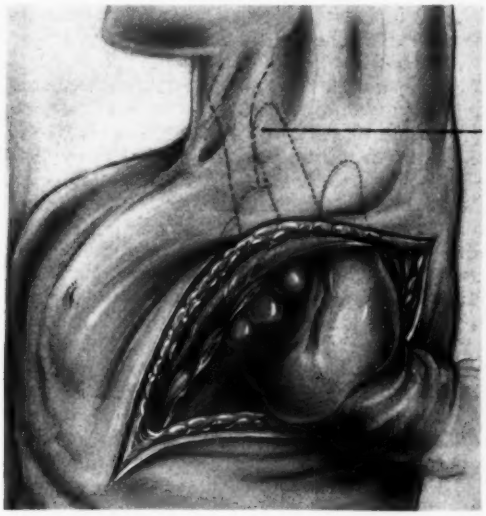

Fig. 9. Dissection with the index finger extends to the cervical region above the isthmus of the thyroid gland (shown by dotted line).

Fig. 10. Exteriorization of the esophagus with the tumor, by simple traction. Removal of the tumor. Dotted line in inset indicates new position of esophageal stump.

incision includes the skin and cellular subcutaneous tissue. The wide muscles of the dorsum are divided down to the costal skeleton (Fig. 3). Careful hemostasis is maintained throughout the operative procedure.

The seventh rib is removed in almost its entire length, from the posterior angle to the neighborhood of its anterior end. About 8 centimeters of the sixth and fifth ribs are excised from the posterior angle forward (Fig. 4). The soft parts of the fifth and sixth intercostal spaces are excised between ligatures. The parietal pleura is opened in its entire length following the axis of the wound (Fig. 5). An Arce retractor is used to help to maintain the thoracotomy wide open. The lung is completely collapsed. A small quantity of serous fluid is usually present in the pleural cavity.

In front of the thoracic aorta, a few centimeters above the diaphragm, the mediastinal pleura is incised (Fig. 5). This incision is extended upward to the aortic arch. The esophagus is isolated by blunt dissection, and the tumor which has become a part of the esophagus itself is recognized (Fig. 6). In this case the tumor was attached to the bronchoaortic arch. All the healthy portion of the esophagus situated underneath the tumor is isolated from the cellular tissue of the mediastinum and the tumor is separated from its peripheral attachments by blunt dissection with the end of the index finger (Fig. 7). The esophagus is sectioned about 3 centimeters from the cardia after being crushed and doubly ligated. The inferior end is buried beneath a pursestring suture which is made by using the gastric wall. The superior end is protected with a piece of gauze (Fig. 8).

Dissection of the tumor is completed at the level of the bronchoaortic region. Any fibrous attachments must be excised with scissors. Bleeding produced by this dissection is slight and is spontaneously controlled.

The mediastinal pleura is incised in the supra-aortic portion as the index finger lifts a fold of it. This incision is extended to the dome of the thorax. Digital dissection of the supra-aortic portion of the esophagus is carried out. The entire organ is then passed beneath the aortic arch and exteriorized through the incision in the mediastinal pleura

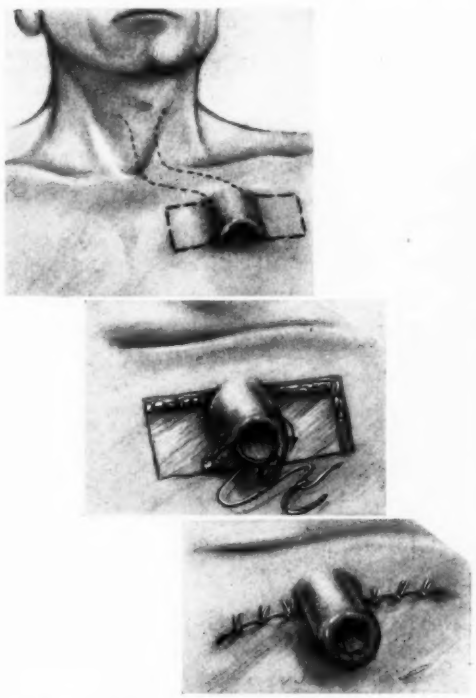

Fig. 11. Building of the "gargoyle" to insure accommodation of esophagus and the India rubber tube.

situated above it. The passing of the esophagus through the narrow passage situated underneath the arch is done by pulling its supra-aortic portion, and not its inferior tied end, and of course without folding it upon itself.

Once this passage is accomplished digital dissection is continued in all the upper portion of the thoracic and cervical esophagus (Fig. 9). The index finger introduced through the supra-aortic incision of the mediastinal pleura makes this step in the operation very easy.

We would emphasize the fact that if the operator stands at the ventral side of the patient—a step not described previously—he is afforded better visualization of the esophagus thus facilitating dissection. Also, in this position it is always possible to use the right hand to free the esophagus from the thoracic walls.

The thorax is closed and the dissected esophagus is left with the tumor still inside (Fig. 10). This closure is final. The mediastinal pleura is not sutured. The parietal pleura is sutured. The costal wound is approximated with two thick silk sutures. The muscles of the dorsum are closed with catgut. The subcutaneous cellular tissue is sutured. The skin is closed with interrupted silk sutures. While the wall is being closed, the anesthetist distends the lung progressively using high pressure in a closed circuit with the Foregger anesthetic apparatus, oxygen only being used, no anesthetic. The thorax is not fully closed until the lung can be seen completely distended, filling all the thoracic cavity. Then the thorax is closed without drainage.

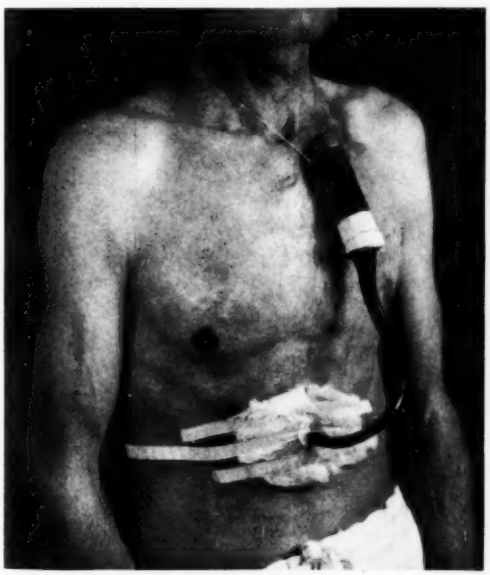

Fig. 12. Photograph of the patient with apparatus in position.

Fig. 13. Roentgenogram of the thorax 5 months after operation. In the left side can be seen, below the clavicle, shadow of the "gargoyle." Metastasis is not evident.

The thoracic wound is covered with gauze, and the patient is placed in supine position with the head extended and turned to the right side. Local anesthesia is used. An incision is made following the anterior margin of the left sternocleidomastoid muscle. Incision includes the skin, subcutaneous cellular tissue, and cutaneous muscle. The sheath of the sternocleidomastoid muscle is opened at the level of its anterior margin. The muscle is pulled outward and the posterior leaf of the sheath is separated, thus revealing the cervical esophagus. This dissection is very easy because of the blunt dissection which already has been done via the thorax (Fig. 10).

All of the thoracic esophagus is exteriorized through the cervical wound by traction in its cervical portion.

The esophagus is excised about 3 centimeters above the tumor. By blunt dissection a tunnel is built beneath the skin of the anterior aspect of the superior portion of the thorax. In the lower end of this tunnel which is almost vertical, a transverse incision 3 centimeters in length is made in the skin. The stump of the esophagus is intro-

duced through this tunnel and its terminal opening is sutured with silk to the cutaneous wound. The cervical wound is closed in two layers (Fig. 10).

During operation the patient remained in exceptional condition from both respiratory and circulatory standpoints. There was no dyspnea.

The mediastinal maneuvers produced some circulatory disturbance as evidenced by tachycardia and hypotension. Nevertheless the tachycardia did not at any time exceed 120 pulsations a minute. During the operation 500 cubic centimeters of physiological salt solution was injected in a vein.

At the end of the operation the circulatory condition of the patient was satisfactory. Pulse was 120 a minute. A blood transfusion of 500 cubic centimeters was carried out.

After operation, the patient had a rise in temperature from the first day, the temperature fluctuating between 37 and 39 degrees C.; the pulse stayed between 120 and 130 a minute. Routine therapeutic measures were carried out; saline and glucose solutions were administered; cortical suprarenal extract was given in large doses. A fairly normal diet was maintained by means of the gastrostomy.

On November 4, 6 days after the operation, pleural collection was evident and was confirmed by the x-ray picture. A small thoracotomy was performed through an intercostal space to introduce a Pesser catheter No. 20 and 1750 cubic centimeters of serosanguinolent fluid was drawn. Drainage was maintained. Examination of the liquid obtained showed the following: a few staphylococci and Gram positive diplococci were observed; a normal quantity of degenerated leucocytes and abundant normal erythrocytes were also observed.

The temperature continued to fluctuate between 37 and 38 degrees for some days more with a corresponding variation in pulse. Any movement caused tachycardia which, however, improved little by little. Outside of these abnormal periods the pulse stayed between 100 and 110 a minute. Under these circumstances Dr. Marcelino Campana, who had been of great help during the postoperative period, advised the use of arterocolina. This therapeutic measure was very effective.

The wounds of the esophagostomy and of the thoracotomy healed *per primam*. Because the saliva flowing continually through the esophagostomy irritated the skin and to secure a better means of feeding the patient, on November 11, a connection was established, by means of a rubber tube, between the upper stump of the esophagus and the gastrostomy opening. The tube worked well and the patient was able to eat in the natural way.

The rubber connection functioned well for a period of more than 10 days; it served not only to feed the patient but also to direct the saliva toward the stomach thus preventing it from going through the esophagostomy. Little by little, however, the esophagus became ulcerated a little above the clavicle, and a subacute cervical cellulitis was produced. Once the tube was withdrawn the cellulitis improved, but in the supraclavicular region a small esophagocutaneous fistula persisted that did not tend to heal. We then used a suction pump to effect continuous suction of the saliva. The fistula closed in a few days and the skin returned to normal condition.

A pleural suppuration, caused by the silk threads which approximated the ribs, made necessary the removal of the sutures under local anesthesia.

At present, 5 months after the operation, the patient is well. He gained 13 pounds in weight and nutrition is good. The red and white blood cells are again normal.

To secure a more perfect fitting between the esophagus and the India rubber tube, on January 30, 1941, we covered the esophagus with skin. Thus, we formed a sort of gargoyle which is introduced in the India rubber tube (Figs. 11 and 12). The feeding of the patient is satisfactory. It has not yet been decided to build a prethoracic esophagus. We intend to do this once the usual period of recurrence has passed.

(Complete bibliography is to be published in a later issue of *Boletin del Instituto de Clinica Quirúrgica.*)

(Translated by Miss E. R. Sala, secretary, Institute of Surgery, Buenos Aires.)

LUNG INJURY DUE TO THE DETONATION OF HIGH EXPLOSIVE

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TO the neutral observer this war is truly different from previous struggles; different in its conception of attack and defense, as well as in the vulnerability of the civilian population. As a result of the development of the bombing attack, attention has been directed to new problems of war injury. Numerous reports have appeared concerning the effects of detonation of high explosive. And attention has been called to the fact that many deaths occur without evident gross injury to the body, while the necropsy reveals varying degrees of trauma to the lung. Many clinical and experimental studies have been made on the differing types of injury due to "*blast*" and the results appear to have given rise to varying conclusions. Moreover, in recent discussion appearing in the American literature little or no attention has been directed to this form of lung injury. It is, therefore, the purpose of this paper to review critically the recent clinical and experimental studies that have been made on the effects of detonation of high explosive, particularly on the pulmonary system, and to compare them so far as possible with the "similar" forms of lung injury as observed in peacetime civilian life.

PEACETIME INJURIES OF THE LUNG

Lung injury in the intact thorax, apart from a few isolated cases, has received but little mention in the English surgical literature. Its occurrence was recognized and described as early as 1761, when Morgagni reported two postmortem findings. Richter, in 1904, and Schwartz and Dreyfus in 1907, each gave a good account and a review of the current literature, and Fischer wrote an excellent monograph in 1912.

Thoracic injuries are to a certain extent comparable with those of the abdomen and skull in that attention is devoted less to the parietal lesion than to the possibilities and extent of damage to the contained viscera (Smith, 1840; Sellors, 1933). Many of the cases reported were the result of severe crushing violence to the chest and the diagnosis was not usually made until postmortem examination.

Physiological anatomy of the thorax. Most writers are agreed that injury to the thoracic viscera is more frequent in children and adolescents and that this is resultant to the elastic nature of the juvenile thoracic cage. It has been suggested that the lung is simply compressed between the more resilient ribs or against the vertebral column.

In a series of experiments on the thorax after removal of the contained viscera, Triepel (1902) made the interesting observation that the male thorax can withstand more lateral and the female more sagittal pressure. Kulbs (1909), in his animal experiments, found that the chest yields more to a blow from the front and, as a whole, is less capable of resistance to this injury. Compression of the thoracic cage, according to Limón and Pera (1921) causes immediate diminution in its size, primarily at the expense of the mobility of the costovertebral and costosternal joints. When the motility of these joints is insufficient, a new factor intervenes which is determined by the elastic properties of the costocartilaginous cage.

The presence of air within the lung at the time of injury was discussed by Gosselin (1845), Gross (1866), LeConte (1908) and Adams (1933). It was pointed out that sudden compression of the air within the lung causes the lung to rupture owing to the resultant instinctive closure of the glottis, together with the withholding of breathing, thus making it impossible for the pulmonary sponge to empty.

Peyrot (1907) stresses the anatomicophysiological arrangement of the pleura. The normal cohesion of the pleural surfaces holds the lung to the parietes. Thus, if the chest wall with its parietal pleura and the lung with its visceral pleura are depressed, the remainder of the lung is prevented by its natural adherence to the chest wall from following the movement. A part of the organ which is seldom stretched is thereby put under tension and tears may result.

From the Department of Research Surgery of The Ohio State University. Dr. King, Comly Fellow in Research Surgery, served as surgeon to the First Base Hospital for the Chinese Army at Shanghai during its repeated bombing and eventual capture by the Japanese in 1937 (G.M.C.).

Fig. 1. Gross appearance of the lung after injury by contusion in peacetime civilian life. Note the scattered areas of hemorrhage.

Du Séjour (1901) agrees that the mechanism stressed by Peyrot would explain rupture if the pleura were adherent, but thinks otherwise, that there is too much gliding between the pleural surfaces. In his opinion the air-filled lung is abruptly compressed at the time of trauma and escape of the air through the upper air passage is insufficient. Hence rupture results by sudden compression as one might burst an inflated paper bag. Similar opinion was expressed by Gross (1866).

Joannides and Tsoulos (1930), after experimental work on the production of mediastinal emphysema in dogs, came to the conclusion that "anything which produces an increased intrapulmonary pressure, such as a severe cough, the labor of childbirth, lifting of a heavy weight, etc., probably causes a mild degree of mediastinal emphysema and air embolism, which as yet we have no way of recognizing clinically."

Morbid anatomy after injuries. The morbid anatomy of the injuries varies greatly. In simple contusion, bleeding occurs into the lung substance, as Duval (1918) has shown, producing areas of contusion at the base and apex of the injured lung, with blood infiltration of varying extent—simple contusion by *contre-coup*. Duval even demonstrated small tears of the visceral pleura on the opposite side.

Rupture of the alveoli with interstitial emphysema about the capillary vessels was also noted recently in the animal experiments of Adams (1933) carried out by simulating a submarine escape. Sometimes the hemorrhage is severe and may be localized to one lobe as in an instance reported by Sauerbruch (1937). It can be even more marked, as in the case of Rocher and Dupérié (1927) which is typical of gross hemorrhagic infiltration of both lungs without apparent tears in the pleura. Similar observations were also reported by Duval.

Fischer (1912) gave an anatomical classification of rupture of the lung according to the severity and site of the lesion: (1) Crushing into a shapeless mass of one lobe of the lung or of the whole lung; (2) internal rupture of the lung with intact visceral pleura; (3) complete penetrating rupture of the lung; (4) separation of one lobe of the lung.

Cooke (1936) more recently presented a clinical classification of pulmonary injuries: (1) the pneumothorax type; (2) parenchymal rupture—this is a simple rupture without laceration of the visceral pleura; (3) combined types.

Tears of the larger bronchi are known to occur (Davis, 1891), and are compatible with life provided the patient survive the immediate effects of the injury (Davies 1930, Clerf 1940).

Lung injury without trauma to the thoracic cage may be produced by the following causes: (1) Run over by a heavy vehicle—accounts for 22 out of 70 cases in Fischer's series—Watson, Smith, Tatum, Johnson, Harlan, McDonnel, Ashhurst, Laurent, Kerr, Mercadé, Richter, LeConte, Villegas, Sauerbruch; (2) blow on the chest—Davies, Bogdan, Spiers, Payne, Scott, Connolly, Dieffenbach, Head, Fallon; (3) fall from a height—Gosselin, Gross, Wharry, MacTaggart; (4) lifting a child by the arms—Cockle; (5) glancing blow of a bullet—Rees; (6) increase in the intrapulmonary pressure by: coughing—Stransky, Sauerbruch, during parturition—Cunnington, dyspnea during tracheotomy—Werwath, violent respiratory effort—Waters; (7) nearby explosion—Delacroix, Ravaut, Thomas, Sencert.

ILLUSTRATIVE CASE REPORT

An example of this type of injury from our own records is presented as follows:

Autopsy No. 1238–1581 (Arch. 1097). White boy, aged 12 years. The history relates that he was playing with two other boys at the city gravel pit. They built a cave in the side of some loose shale. The roof suddenly caved in and the boy sustained a heavy crushing blow on the chest by large pieces of falling shale and loose earth. When dug out he was found bleeding from the nose and was brought immediately to the hospital. He was pronounced dead upon reaching the hospital.

On examination blood was found in the ears, nose, and mouth. No other abnormality was found. The clinical diagnosis was fracture of the skull.

Postmortem examination revealed fracture of the base of the skull. The left lung weighed 350 grams. The pleura was unusually hemorrhagic. The lung was expanded and many small hemorrhagic spots appeared scattered over its pleural surface. On its cut surface appeared numerous areas of petechial hemorrhage. The bronchi were filled with foamy blood. The right lung presented identical changes (Fig. 1).

Microscopic examination of the lungs revealed multiple areas of hemorrhage of varying size scattered throughout the entire lung. Many of the alveoli appeared disrupted and filled with red blood cells. The bronchi and bronchioles were also filled with red blood cells (Fig. 2).

This is an instance of peacetime injury of the lung without evidence of external injury. It was not recognized clinically. The fact that extensive visceral damage can be produced without revealing any *external* evidence is important from many points of view. The clinical significance of this example is obvious and has been recognized by certain surgeons.

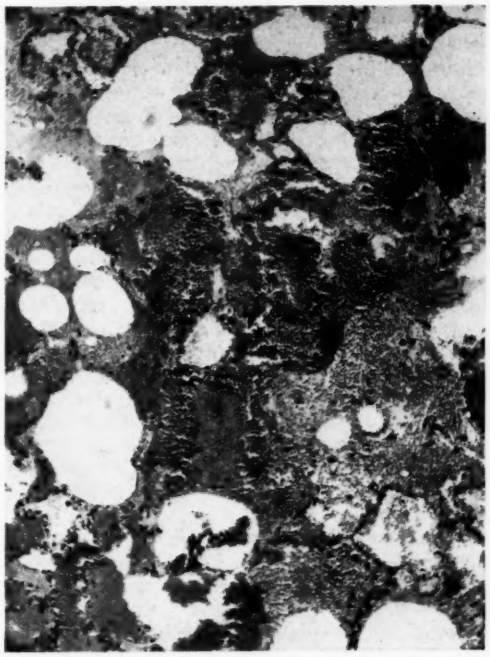

Fig. 2. Photomicrograph of the lung appearing in Figure 1. Note the hemorrhagic exudate in the ruptured alveolar spaces.

THE NATURE OF HIGH EXPLOSIVE EFFECTS

Having reviewed traumatic lung injuries without external lesion as they are encountered in peacetime civilian life, it remains to compare them with the lesions produced by the detonation of high explosive. Many have a vague knowledge of the nature of explosives. This doubtless explains their ready acceptance of fantastic stories of the discovery of explosives of extraordinary power, tales of which are so often circulated.

"Explosion" has been defined as "the act of exploding; a rapid combustion, decomposition or similar process resulting in a great and sudden development of gases, and consequent violent increase of pressure, usually causing a loud report."

"Explosive" is any substance that may cause an explosion by sudden combustion or decomposition. Two categories are recognized, low and high explosives. Low explosives are those having explosion velocities of a few thousand feet per second or less. Members of this group are characterized by a comparatively slow "push" type of explosive effect. High explosives are those having explosion velocities of from 5,000 to 25,000 feet per second and, consequently, have quite a different effect. The violence of their detonation produces an extreme shattering effect in the immediate vicinity.

"Detonation" is a violent explosion: one resulting from practically instantaneous decomposition or combustion of unstable compounds.

A "bomb" has been defined as "a hollow projectile of iron, generally spherical, containing an explosive material which is fired by concussion or by a time fuse: also any similar receptacle of any shape containing an explosive: as a dynamite bomb" (Muehlberger, 1937).

The British speak and write of the immediate effect of the detonation of a modern high explosive bomb as "blast."

The chemistry of high explosive. High explosives depend for their action upon the instability of the chemical equilibrium of their constituents. They consist of compounds of carbon, oxygen, nitrogen and hydrogen so feebly combined that when fired by combustion or detonation, new, simpler and more stable gaseous compounds are formed. Once chemical action is started it proceeds with great velocity and the explosive is immediately converted into gases with the evolution of heat. These

gases, now occupying an enormously greater volume than the original substance, have powerful distintegrating properties. High explosives are violent, detonating at the rate of several miles per second, many times greater than the speed of the most violent hurricane (Bloxam, 1882; Logan, 1939; Storm, 1939).

The nature of "blast." By "blast" or explosion is further designated the compression and subsequent suction wave which is set up by the detonation of high explosive. At every point in the immediate neighborhood there occurs first a momentary wave of high pressure (for about 0.006 seconds for a 70 pound charge) and then a negative "suction" pressure due to the fact that the positive compression wave has reduced the density of the air behind it to below normal atmospheric pressure. Like the pressure component, the suction component of the blast wave lasts but for a fraction of a second, yet as a rule for a longer period than the compression wave (up to 0.03 seconds for a 70 pound charge).

The wave of pressure is highest in the immediate region of the explosion and falls off rapidly as it moves away. Thus 15 feet from a 125 pound charge, the hydrostatic pressure may be of the order of 200 pounds per square inch, whereas 50 feet away the maximum pressure recorded will not be more than 10 pounds. Everything in the immediate neighborhood of the explosion of a big bomb will therefore be suddenly exposed to a violent pressure wave of many times atmospheric pressure, whereas everything 50 feet away will be exposed to only two or three atmospheres of pressure.

The suction component of the blast wave is always weaker than the pressure component and in no case can it be greater than 15 pounds per square inch, since this corresponds to a complete vacuum. The magnitude of the pressure and suction components of a blast wave are correlated directly with the amount of explosive and are much higher for larger than for smaller amounts (Roomary, 1910; Taylor, 1932; Zukerman, 1940).

The physics of "blast." The prime characteristic of any form of wave motion is that whereas the disturbance itself moves forward, the particles of the medium through which it passes do not move with it, but oscillate backward and forward about the position of equilibrium. The plane of oscillation may either cross the line of propagation, called transverse waves, or parallel the line of propagation, called longitudinal waves.

For the sake of simplicity imagine that the origin of the blast is a small sphere of explosive material. When this is detonated it expands suddenly and compresses a spherical shell of air immediately surrounding. Thus the blast wave consists of a compression followed by a rarefaction as it is propagated outward.

The maximum movement of any air particle on each side of its normal undisturbed position is called the amplitude of the wave and clearly depends upon the violence of the explosion. In the case of aerial bomb explosions such as are now being experienced in Europe, the amplitudes are considerable, for in the compression part of the wave pressure up to 200 atmospheres—that is, 1 and ⅓ tons per square inch—have been observed.

The phrase "beating the air" is commonly used to denote ineffectiveness. Beating the air is normally ineffective, because the mobility of the air generally makes it easy for it to escape around the edges of the vulnerable object. The more sudden and violent the "beating" the less is this true, and the more will the air act not like a mobile gas but a rigid object, so that the violence of blast can even bruise the walls of the lung as if they had been hit by a solid object (Berthelot, 1885; Burlot, 1931; Sutherland, 1940).

THE EFFECTS OF DETONATION OF HIGH EXPLOSIVE

The extraordinarily varied effects of bombing on buildings in cities and towns have been vividly described and minutely detailed by Haldane (1938), Langdon-Davies (1939), and others from their experiences in the Spanish War. They described how, when bombs burst in a street, the metal shutters of the shops which had not been hit were sucked outward. When a bomb exploded inside a house a large part of the shattered walls fell inward.

According to Logan (1939), Zukerman (1940) and others, a man may be wounded by a bomb explosion either by being hit by fragments of the bomb-casing or by masonry or some other hard substance falling or sent flying by the explosion; or by being violently thrown; or by being affected by the blast wave without being thrown.

Lockwood (1940), and Logan reported that during World War I (1914–1918), men were sometimes picked up in the field dead from an explosion without revealing any external injury, and sometimes with blood-stained fluid trickling from the nose or mouth. Similar experiences were described by Mogena (1938), Langdon-Davies (1939), and Mitchener and Cowell (1939), in the Spanish War.

Again, in this war there have been reports of the damaging effects of blast on domestic animals. The damage to the lungs, characterized by al-

veolar rupture and hemorrhage, has been the consistent and dominant feature.

CLINICAL INVESTIGATION

Early observations. The literature on this subject is limited because this form of injury was not well known prior to the last war (1914–1918). Nevertheless, the earlier clinical observations had led to the belief that the lesions and death from the explosive effect were due either to gases such as carbon monoxide produced from the detonation of the explosive (Brouardel, 1887; Cénas, 1887; Dujol, 1887; Servel, 1887; Mitchell, 1897; Urie, 1904; Bahier, 1905; Fabre, 1906; Hatton, 1911), or resultant to a sudden vacuum effect in those parts of the body which contain gas; e.g. the lung lobules, stomach, or intestine. Thus, experimentally, gas bubbles may be set free in the blood by the sudden evacuation of a chamber in which an animal is placed. These bubbles may then block the circulation as in compressed air workers or deep sea divers when they are too rapidly decompressed (Bert, 1875; Granjon-Rozet, 1877; Gaudin, 1887; Guinand, 1887; Reynaud, 1887; Thomas, 1917; Hill, 1917).

The earlier clinical observers also reported that this form of trauma produces injuries in the nervous system (Hinchcliff, 1875; Coskery, 1877; Duret, 1877; Michel, 1878; Tryon, 1891; Matignon, 1907; Zangger, 1907; Querleux, 1908; Etonensis, 1909; Llewellyn, 1910; Stierlin, 1912; Claude, 1914; Laurés, 1915) and in the lung (Reynaud, 1887; Paucot, 1901; Delacroix, 1907; Ravaut, 1915; Thomas, 1915; and Sencert, 1915).

Recent observations. Gatti (1918) presents a case of acute paralysis with subsequent atrophy following the explosion of a large bomb without actual contact. The condition was similar to that seen in anterior poliomyelitis and the assumption is made that the concussion injured the motor portion of the spinal cord. Similarly Cramer (1919) reports the case of a young soldier who presented the signs of a severe aortic insufficiency after being thrown several feet into the air by the explosion of a bomb. This patient had previously been healthy and had not had those diseases which might predispose to such a heart lesion.

Mott (1916, 1917) reported several patients as having died of explosive concussions in which two outstanding lesions were observed. First, the hematomas present in the lung, and second, the extreme vascular injury to the brain. He believed that the enormous aerial compression "may be transmitted to the fluid about the base of the brain and cause shock to the vital centers of the floor of the fourth ventricle, causing instantaneous arrest of the function of the cardiac and respiratory centers." This, he held, explained many of the instances of sudden death in which no visible injuries to the body were evident. Similarly Haldane, in describing a personal experience of his own during World War I when he was in the vicinity of bursting shells, thought that death under such conditions might be due to respiratory paralysis. Other similar observations of injury to the nervous system from the effect of explosion were also reported by Chavigny (1916), McWalter (1916), D'Abuno (1916), Meige (1916), Ltermitte (1917), Pachantoni (1917), and Marage (1918).

Mogena (1938) saw several instances of soldiers in Spain suffering from violent "bodily commotion" from proximity to a bursting shell. Examination of those killed by explosion (without obvious external injury) may reveal a tear of the lung, or a bulbar hemorrhage: in others who live for a time, rupture of meningeal vessels, hemorrhage from intestinal laceration and other internal trauma. In some the hermorrhage might not appear for 2 to 3 days. The author explains this as due, in his opinion, to gas embolism from sudden atmospheric decompression.

Falla (1940) reported a case with capillary hemorrhage in both lungs due to blast. The patient died 12 hours following operative intervention for bleeding from a laceration of the thigh after the use of open ether anesthesia (Fig. 3).

Dean and Allison (1940) observed 27 instances, and in all but two evidence of serious or gross pathological changes in the chest was absent. They called attention to the relative disproportion in frequency between the symptoms and physical signs in the cases studied, the frequency of a ballooned appearance of the chest and the radiological appearance of a diminution of rib-expansion. A similar observation was made by Rose (1940).

Roberts (1940) pointed out the contraindication to surgical operation. Of two patients whose abdomens had been opened for intense abdominal symptoms, neither presented any demonstrable lesion and the thoracic injury appeared to be the real cause. He calls attention to the fact that if a group of bomb casualties contains one blast case it probably also contains others, even though the signs and symptoms are lacking.

Hadfield et al. (1940) reported 10 cases of sudden death in persons subject to the blast effect of high explosive bombs. In none of these was there any evidence of external trauma. There were gross hemorrhagic lesions in both lungs in all, and blood stained secretions in the upper air passages in

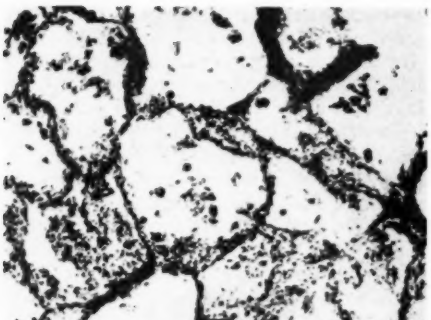

Fig. 3. Photomicrograph of the lung of a man who died as a result of injury sustained in an air raid (Falla's case). The alveoli, which are disrupted, are filled with blood cells. (After Zukerman.)

some. Again they reported a case in which a man aged 23 lived for 51 hours after exposure to a blast. As a result of this observation they believe that patients who develop pulmonary hemorrhage without external trauma to the thoracic wall continue to bleed into the lung for a period which may amount even to 48 hours. In the light of the postmortem finding of continued bleeding they concluded that these patients should be rested as strictly as if they had had recent severe hemoptysis (Fig. 4).

O'Reilly (1941) stated that from 3 cases which he had studied one clinical point had emerged; that within 48 hours in 2 and within 4 days in the other the clinical findings of an ordinary lobar pneumonia had apparently developed. Again 5 patients belonging to the same "incident" were brought in with the appearance of acute abdominal catastrophe—rigid abdomen, pain, and so on. Two were sufficiently serious to require surgical intervention, but nothing was found except a few minute subserous hemorrhages.

Ross (1941) made a comparative postmortem study of peacetime and wartime lung injuries and concluded that the main points of difference may be summarized as follows:

1. In compression asphyxia the lesions may be symmetrical on both sides but not necessarily. The hemorrhages are usually subpleural and in the lines of the ribs. There is generalized pulmonary congestion.

2. In hemorrhage due to impact of a solid the hemorrhage is in relation to the point of maximum impact and may be unilateral. The lung tissue is contused, torn, and filled with blood at or around this point.

3. In "hemorrhagic concussion" (due to blast) the lesions are always bilateral and roughly symmetrical. There is general congestion of the lung. Pleural hemorrhages are present only as an extension from deeper areas.

Osborn (1941) from the results of his comparative study of peace and wartime injuries to the lungs states that there are two forces which bring about the capillary hemorrhage in "hemorrhagic concussion." These are compression of the lungs through the chest wall and diaphragm and the counterpressure exerted by the air in the alveoli. The actual lesion is mainly hemorrhagic from the alveolar capillaries. The lesion itself is not progressive, as Hadfield et al. claim, but the reaction is. Treatment is largely in the anticipation of complications.

In conclusion he states that "to understand the lesions described for blast in animals and men there is no need to assume that blast has any mysterious properties. It is only a more severe diffuse sudden compression of the chest and abdomen than we see in civil cases during peacetime."

Robb-Smith (1941) after the study of 789 consecutive accident cases of all types again called attention to the fact that "the pulmonary symptoms which arise from exposure to the blast of high explosive may be due to a combination of pulmonary concussion and fat embolism, and fat emboli should be specifically looked for in autopsies on air raid casualties." A similar observation was also reported by McKibben (1919) from his experimental study.

Experimental observations. The prevailing idea formerly was that the nervous system was especially sensitive to this form of trauma. This received the support of Mott and others. However, clinical and postmortem observations have now established that the pulmonary lesions predominate.

Carver and Dinsley (1919) report experiments on fish, rats, and mice. They state that the animals which were more exposed to detonation showed hemorrhages from the ears, nose, and mouth and when sacrificed exhibited varying degrees of internal hemorrhage in the viscera and central nervous system while the alveoli of the lungs were nearly always found to a certain extent ruptured.

Mairet and Durante (1919) have published several reports concerning concussion shock, the last of which presents their conclusions and opinions based upon a considerable amount of experimental work. They exposed rabbits to the detonation of high explosive under various conditions and made a particular study of the resultant lesions. The symptomatic behavior of the animals was also noted. The viscera of the animals at necropsy were found to be normal except for the lungs which were spotted with hemorrhagic areas. On the surface of the cord in all cases they found varying amounts of blood suffusion, irregularly distributed, with small clots adhering to the nerve roots. The brain appeared normal or showed petechial hemorrhages at various points on the surface. Upon these observations they developed a theory that concussion shock is due to vibrations set up in the atmosphere which, transmitted to the organism, act injuriously by violently agitating the unprotected tissues.

Hooker (1923) determined the physiological effect of air concussion. Experimental observations were made upon dogs, cats, rabbits, and frogs exposed at various distances to small charges of explosive and to gun-blast. According to this investigator, bruising with rupture of the lungs was the single gross lesion found postmortem, and this lesion was probably the primary cause of death when it occurred.

Barcroft (1940) also investigated the physiological effects of "blast" and established four points from his experiments: (1) that only animals placed in the open and within 15 feet from the exploding bomb suffered ill effects; (2) that the Anderson shelter gave immunity at 15 feet and outward to "blast" injuries; (3) that the animals situated further than 15 feet suffered no demonstrable lesion of their organs; and (4) that the lesions found in the animals nearest to the explosion were essentially in the lungs. Histologically, these lesions consisted of bruising of the lung surface along the line of the ribs and vertebral borders, and extended for one-quarter to one-half inch into the lung tissue. Other small hemorrhages were found deeper, especially around the small bronchi. From a study of animals observed over a subsequent period of weeks, the exposure to "blast" appeared to have had no permanent effect.

Until recently, the manner in which the pulmonary lesions are caused by the "blast" had not been studied. Various workers have, however, speculated about this on the basis of the character of the lesions, and three possibilities have been suggested: The first is that the lesions are due to the lowering of alveolar pressure by the suction wave, acting through the respiratory passage with the consequent rupture of the alveolar capillaries. The second is that the lesions are caused by the distention of the lungs with air. The third is that the lung lesions are due to the impact of the pressure wave on the chest wall.

Fig. 4. Cut surface of the lung of a girl found dead in a public shelter which received a direct hit by an aerial bomb. Note the distribution of the hemorrhages which are most extensive in the deeper parts. (After Hadfield et al.)

Zukerman (1940) in a recent, more elaborate investigation designed to determine the mechanism by which the lung lesions were produced, confirmed the extensive injury to the lung tissue in a wide variety of animal species. The view which his experiments substantiated was that the lesions were due to the impact on the thoracic wall of the pressure component of the blast wave. Rabbits were exposed to the explosion of hydrogen and oxygen in balloons. When very close to the bal-

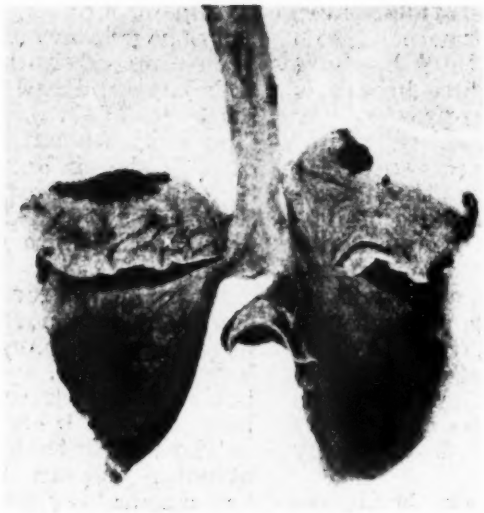

Fig. 5. Moderately severe hemorrhages in the lungs of a rabbit exposed to blast. (After Zukerman.)

loon, the lesions were found mainly or entirely localized on the side facing the balloon. It appeared to be a direct impact effect, and not some more general pressure effect through the trachea. In the latter instance the lesion would be expected to be bilateral. In another set of experiments one-half of the animal was covered with sponge rubber; if the covered side were placed toward the explosion the animal sustained practically no lesions, but if the covered side were away from the explosion it received many lesions on the uncovered side facing the explosion.

Near the explosion of a 70 pound charge (at 13 to 18 foot distance) the animals would be found dead within one minute. At these distances the positive component of the blast wave (hydrostatic pressure) varied between 126 and 63 pounds per square inch. Further away, in a zone of lower pressure (at 18 to 20 feet) the animals would die, as a rule within 24 hours. The clinical features were fairly constant, including air hunger and dyspnea. Still further away was a zone (at 20 to 50 feet) in which the animals survived and recovered, and in which they showed no external appearance of injury, though postmortem examination revealed characteristic visceral changes.

In none of the animals which died was there any external sign of injury, and in no case were fractures observed. The predominant lesion was bilateral traumatic hemorrhage in both lungs varying in degree according to the distance of the animals from the explosion (Fig. 5).

Microscopically, the lesser degrees of damage appear as a small zone in which the alveoli and the smallest bronchioles are filled with blood. The alveolar walls are often disrupted, the hemorrhage originating in the torn alveolar capillaries. In severe grades of damage, large areas of the lung are disrupted and hemorrhagic and the larger bronchi become filled with blood (Fig. 6).

No changes were observed in the other organs and tissues of the body. Zukerman concluded by emphasizing that in the case of fatal injuries due to blast, "what actually caused death in such cases—in fact, what caused death in experimental animals subjected to blast alone was not known, and it was to the solution of that problem that some experiments at the present were being directed."

Stewart et al. (1941) more recently report their experimental investigation of blast injury to the central nervous system. Again, they emphasize that lesions of the central nervous system may be produced. They state that "though pulmonary damage is apparently a constant finding and at times is very extensive, it seems unlikely that it is responsible for either sudden death or later fatalities except in a contributory way." They suggest "that the mechanism responsible for the cerebral lesion was the hydraulic-like pressure on the central nervous system, in its firm encasement, resulting from sudden compression of the thoracic cage with consequent violent back-pressure on the venous side."

TREATMENT OF THE INJURED

Prevention. On the basis of both the clinical and experimental observations it may be stated that prophylaxis is possible. And there are two measures of direct importance in the prevention of this form of trauma:

First is the application of the general principle of protection from the blast wave by the use of air raid shelters and the like such as ditches, holes, and gutters on the ground. As an emergency measure one should lie flat on the ground in the prone position, since the back yields less to injury than the front part of the chest.

Second is the application of some direct measure of protection by covering the chest with sponge rubber or some similar material.

Management after the injury. The importance of early recognition of the lung injury, in order to treat it rationally, cannot be overemphasized. If, for example, as the result of careful clinical observation it is concluded that pulmonary lesions are

present in those whose degree of shock is out of proportion to the apparent severity of the injury, then the indication will be to avoid unnecessary operative intervention and open anesthesia and to concentrate on the treatment of the shock.

It is too soon to determine in full the treatment which may be required. *Complete rest* is essential; and in view of the condition of the lungs found at necropsy and the embarrassed breathing clinically, every effort should be made to avoid any additional trauma and work that might be added to the already traumatized lungs. Oxygen therapy would consequently appear to be worthy of more extensive use. Above all, an awareness that such damage to the lungs may occur should stimulate all concerned to be watchful for this hidden type of danger among those injured in air raid casualties.

SUMMARY

This war differs from those preceding in that aerial bombing has assumed a dominant rôle in the attack. Consequently, the civilian population is, at least in certain phases of the struggle, more vulnerable to attack than the military personnel. This new technique of warfare has created other problems of injury and particularly to the lungs; however, lung injury in the intact thorax occurs more frequently during peacetime than has been formerly recognized and reported.

The pertinent physiological and morbid anatomy of the thorax is reviewed. A case of lung injury unrecognized clinically and discovered at postmortem, similar to that of the lung injury from blast is presented. A brief review of the power of high explosive, and of the nature and physics of the explosion is presented. The outstanding clinical findings of blast injury to the lungs are as follows:

Symptoms may vary from a slight degree of respiratory distress to a complete cessation of respiration depending on the degree of injury inflicted by the blast wave. In general, varying degrees of shock are present accompanied by dyspnea. Cough and hemoptysis also are frequent. Symptoms referable to abdominal and cerebrospinal nervous disturbances have been reported.

Physical examination reveals, in general, no gross injury particularly pointing to the thorax. However, one clinical aspect of importance dealing with this type of injury that demands constant attention is that the gross lesions found elsewhere in the body must not be allowed to overshadow the possible lung injury which is now known to be probable without evidence of external injury to the chest. The importance of this special precaution, clinically, cannot be overemphasized. The presence of blood in the nose or mouth and bloody sputum, and the characteristic x-ray appearance of the chest are of considerable diagnostic importance.

The *postmortem findings* always reveal extensive hemorrhagic lesions in the lungs. All cases show general pulmonary congestion. Pleural hemorrhages are present only as an extension from deeper areas.

The results of the experimental studies carried out by various investigators have confirmed the clinical and *postmortem* findings that pulmonary lesions predominate. The view substantiated by the recent experiments is that the lesions are due to the impact on the thoracic wall of the pressure component of the blast wave. More recent studies have again called attention to the evidence that lesions of the central nervous system may be produced by blast. It has been suggested that the mechanism which is responsible for the cerebral lesion was the hydraulic-like pressure developed from sudden compression of the thoracic cage with consequent violent back pressure on the venous side.

Prevention of this form of injury is better than treatment. Both the general and direct measures for prevention have been discussed. The principles of treatment have been discussed in the light

Fig. 6. Photomicrograph of the lungs of a rabbit exposed to blast, showing many alveoli filled with blood cells and the disrupted alveolar walls. (After Zukerman.)

of the available clinical and experimental observations and attention is called to the necessity of keeping in mind this type of lung injury regardless of whether injuries are found elsewhere in the body.

CONCLUSIONS

1. Lung injury without external evidence of trauma occurs more frequently in peacetime than has been recognized and reported.

2. In a bomb explosion the pressure wave of the blast may produce pulmonary lesions without resultant evidence of injury to the thoracic cage. The lesions are principally due to the impact on the body wall of the pressure component of the blast wave. That this form of trauma produces lesions predominantly in the lung is now abundantly confirmed.

3. It appears that the mechanism responsible for the cerebral lesion is the hydraulic pressure on the central nervous system, in its firm encasement, resulting from sudden compression of the thoracic cage with consequent violent back pressure on the venous side, and that this mechanism may prove to be the explanation for the cause of sudden death in certain cases reported.

4. Prevention is better than treatment; the necessity of providing adequate general and direct protection, particularly to those who are prone to exposure to the bombing attack is evident.

5. After injury complete rest is essential. Every effort should be made to avoid any additional trauma and add extra work to the already damaged lungs. Oxygen therapy should be used more extensively.

6. The knowledge that such damage to the lungs may occur should stimulate all to be watchful for this type of injury especially among air raid casualties.

7. This review by no means concludes the problem of lung injury due to the detonation of high explosives. It is hoped that present and future investigations will bring greater and more accurate knowledge.

(A complete bibliography will be contained in the reprints of this article.)

CAUDAL ANESTHESIA

Its Use in Obstetrics

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FOLLOWING the successful use of caudal anesthesia in proctological operative procedures at the Milwaukee County General Hospital, its adaptability to the obstetrical service was tested. A brief review of the first 400 cases of series in which it was tried is presented.

HISTORY

In 1895, Corning first suggested the possibility of introducing an anesthetic solution into the epidural space. In 1905, Cathelin, a French urologist, blocked the sacral and coccygeal nerves through the sacral hiatus (22). Four years later, Stoeckel used caudal anesthesia with some success in obstetrics. His technique was improved upon by Laewen and Schlimpert, in Germany in 1910. In America, Meeker and Bonar used it successfully in gynecology, in 1923; others followed: Oldham in 1925, Lundy in 1928, Henry and Jaur in 1929, Rucker in 1930, Campbell in 1935, Johnson in 1936, Sword in 1936, and Baptisti in 1939.

DEFINITION

Caudal block, also known as extradural or epidural block, as defined by Labat, consists in passing a needle through the sacral hiatus and depositing an anesthetic fluid within the sacral canal. The solution is distributed outside of the dura mater and the process is thus differentiated from spinal anesthesia, in which the anesthetic is introduced into the subarachnoid space.

Caudal block is not to be confused with transsacral block, obtained by anesthetizing the sacral nerves through the four posterior sacral foramina, which represent the spaces between the fused sacral vertebrae. Presacral or parasacral block on the other hand, is the procedure by which needles are passed through the perineum, anesthetizing the sacral nerves at the points of their exit from the anterior sacral foramina by the deposition of the agent into the hollow anterior aspect of the sacrum. A combination of caudal block plus transsacral block is designated as sacral anesthesia.

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ANATOMY

Throughout the length of the sacrum, the vertebral or spinal canal is continuous as a prismatic space, 6 to 8 centimeters in length, known as the sacral canal. Following the curvature of the sacrum, its anterior and posterior walls are formed by the fusion of the bodies of the vertebrae, and are perforated by the anterior and posterior sacral foramina, through which the sacral nerves course outward. The dural sac, ordinarily terminating at the level of the second sacral vertebra, constitutes the upper boundary of the sacral canal. The lower end of the sacral canal tapers down to the sacral hiatus, an aperture on the posterior surface of the sacrum, usually comparable in size to an adult's thumbnail. This hiatus, due to the embryological failure of development of the spinous process and the laminae of the fifth sacral vertebra, is usually triangular in shape, the apex being designated by the fourth sacral spinous process while the base is bounded laterally by the sacral cornua, bony projections which articulate with the corresponding coccygeal cornua. Not infrequently the hiatus is found to be diamond-shaped rather than triangular. This impression is received when a tubercle, the rudimentary spinous process of the first coccyx, is prominent in the midline and forms the lower angle of the rhomboid. The sacral hiatus is covered by a fibrous membrane, the sacrococcygeal membrane of Cathelin, and by the lateral sacrococcygeal ligaments. The sacral canal contains a loose areolar tissue in which are embedded the filum terminale, the sacral and coccygeal nerves, and a rich plexus of veins.

PHYSIOLOGY

The pelvic and perineal floors are innervated by the second, third, fourth, and fifth sacral nerves and the coccygeal filaments. Both the sensory and motor fibers of these are anesthetized in the sacral canal and, as in spinal anesthesia, the sensory nerves are more readily affected due to their lower threshold for paralysis.

The uterus is innervated by both an intrinsic and an extrinsic nerve supply. The intrinsic plexus, supposedly coursing in the myometrium itself, has been shown to be able to function inde-

pendently of the extrinsic. This has been demonstrated both experimentally in laboratory animals and clinically by the uneventful progress of labor in patients with paraplegias due to cord tumors, transection, or other spinal cord accidents. The intrinsic nerves are influenced by certain factors important for the institution of labor. The hormones, estrogen and progesterone, elaborated by the ovary and particularly the placenta in pregnancy, and pitocin, produced by the posterior pituitary, are necessary for the induction and sustenance of co-ordinated contractions of the uterus. Similarly is the intrinsic supply affected by the mineral ion concentration, particularly of calcium, potassium, and magnesium.

In contrast, the extrinsic innervation of the uterus is derived from both the sympathetic and parasympathetic (cerebrospinal) systems, each of which transmits sensory and motor fibers.

The sympathetic fibers are principally motor in function. Originating in the solar plexus, these fibers traverse the superior mesenteric into the inferior mesenteric plexus, where they unite with fibers from the lumbar sympathetics to form the superior hypogastric plexus (presacral nerve). (That this nerve contains sensory fibers is evidensed by the fact that its resection affords relief in primary dysmenorrhea. However, labor following excision of the superior hypogastric plexus is unaltered.) The superior hypogastric plexus divides to form the bilateral inferior hypogastrics, the hypogastric nerves, which pass downward and laterally, furnishing the main sympathetic root for the pelvic plexus (the uterovaginal plexus, cervical ganglion, or the ganglion of Frankenhauser). Also contributing to the pelvic plexus are branches which are derived from the sacral sympathetic cords and the parasympathetic pelvic nerve, the nervus erigens. This parasympathetic supply to the uterus, the erigens nerve, arises from the second to the fourth anterior roots of the sacral plexus.

From this brief discussion, it becomes evident that the pain of labor, of uterine origin as well as that due to the overdistention of the pelvic tissues comprising the lower portions of the birth canal, can and will be eliminated by anesthetizing the sacral nerves, as is done in caudal anesthesia, while uterine contractions can continue almost unaffected.

TECHNIQUE

The sacral hiatus is rather easily identified. With the right third finger placed on the tip of the coccyx, the right index finger is passed along the midline toward the sacrum, until the inverted V-shaped depression is palpated. The apex of this triangular site is defined by the fourth sacral spine, while its base is marked by the two lateral cornua. Since the sacrum is an immobile structure, the sacrococcygeal articulation can be recognized with the external finger, when the coccyx is moved by a gloved finger inserted in the rectum. To verify the location of the sacral hiatus further, one might visualize an equilateral triangle, with the base line extending between the posterior-superior iliac spines and the apex falling directly over the site for puncture.

The position in which the subject lies for the injection is optional. In our series, both the lateral decubitus as well as the knee chest position were used with equal success. Although the parturient is probably more comfortable lying on her side, the spine assumes a scoliosis, which makes recognition of the bony landmarks somewhat difficult. On the other hand, having the patient kneel, with the elbows drawn as close as possible to the knees, gives the back a symmetrical arch, enlarges the sacral hiatus and exaggerates the anatomical prominences, all of which further facilitate the procedure. Obviously, the knee chest position is more embarrassing and awkward to the pregnant mother; yet, because of its many advantages over the lateral decubitus, it is the position given preference.

The anesthetic being used in our clinic is metycaine (Gamma/2 methyl-piperidino/-propyl benzoate hydrochloride). It is a white powder, readily soluble in water, alcohol, or chloroform. The solutions are stable and retain their potency after sterilization by heating and do not deteriorate on standing. Although experimentally metycaine is more toxic than procaine, clinically this finding has not been substantiated. In its favor, it may be said that metycaine-produced anesthesia is more rapid in its onset and is more enduring than that produced with procaine, and that it is a solution with antiseptic properties of its own. Our results, with the use of a 2 per cent aqueous solution of metycaine without the addition of adrenalin, compare very favorably with those obtained by others, who have tried procaine alone in various dilutions, procaine with adrenalin, with sodium chloride, with sodium bicarbonate, with quinine, with quinine and urea hydrochloride, with magnesium sulphate, and in many other combinations. In our series, the quantity of the solution used varied from 10 to 50 cubic centimeters but for the most part (357 cases), 25 cubic centimeters was used.

The instrumentarium required consists only of a 25 cubic centimeter syringe and an 18-gauge

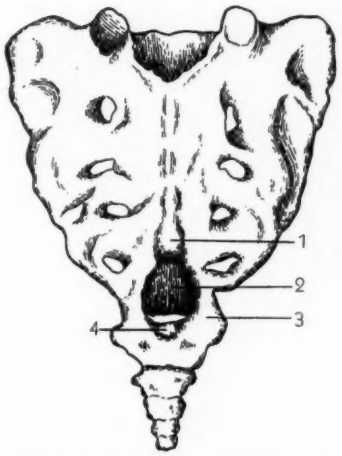

Fig. 1. *1*, Fourth sacral spine; *2*, sacral hiatus; *3* coccygeal cornu; *4*, coccygeal tubercle.

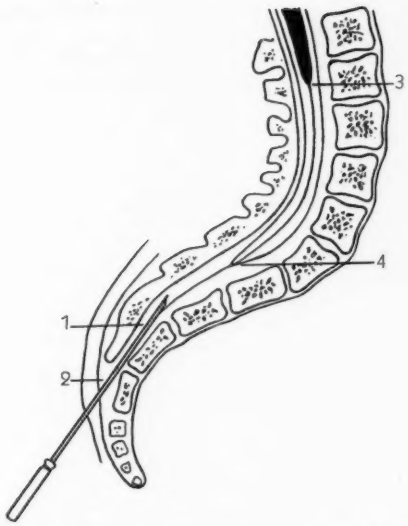

Fig. 2. *1*, Sacral canal; *2*, sacral hiatus; *3*, end of spinal cord; *4*, end of subarachnoid space.

spinal puncture needle with stilette. The operative field is prepared with tincture of iodine or other reliable antiseptic. The sacral hiatus is defined, and the needle is introduced practically perpendicularly into the sacral hiatus. Infiltrating the site for injection with a dermal wheal has been found unnecessary. Penetration of the fibrous sacrococcygeal membrane is announced by a sudden release in the resistance offered, and the point of the needle strikes the anterior wall of the sacral canal. It is then withdrawn a millimeter or two, and the hub is depressed gently, through an arc of approximately 70 degrees, so that the long axis of the needle lies practically parallel to the plane of the sacrum. It is then advanced 3 to 4 centimeters, to insure its presence in the canal. The stilette is withdrawn, the empty syringe is attached and aspiration is attempted. Withdrawal of spinal fluid or blood, signifying penetration of the subarachnoid space or of a vein is an indication for the removal and re-insertion of the needle. The solution is injected slowly, requiring about one minute for 25 cubic centimeters. The development of a tumefaction beneath the skin indicates a subcutaneous rather than an epidural infiltration. The injection completed, the patient is advised to resume the dorsal-recumbent position.

SUBJECTS

In this series of the first four hundred cases in which caudal anesthesia was used, 368 were primaparas and 32 were multiparas. Of the 368 primaparas, 293 were delivered by low forceps and episiotomies, 8 by midforceps and episiotomies (including 1 Duehrssen's incision), 28 were permitted to deliver spontaneously without an episiotomy, 10 delivered spontaneously with a perineotomy, 6 were forceps deliveries without episiotomies, and 20 were breech deliveries—in 4 of which the breech was broken up and extracted. In 17 cases, transverse blades were applied. In 15 of these, Simpson forceps were used; in 2, the Kjelland technique was followed. Seven occiput posteriors failed to rotate after two hours at complete dilatation. Two of these were delivered face-to-pubis; 2 were rotated with Kjelland forceps; 3 were turned, adopting the Scanzoni maneuver. One primapara was delivered by a low cervical cesarean section performed entirely under caudal anesthesia. In one version and extraction, the caudal block was found insufficient and was of necessity augmented by ether. Two of those delivered without an episiotomy sustained a first degree laceration. Two of the primaparas had twin pregnancies. Of the 32 multiparas, 9 had outlet forceps and episiotomies, 4 had a midforceps delivery, 3 were rotated by the Scanzoni operation, 8 were permitted to deliver spontaneously, 4 were delivered by low forceps without an episiotomy, and 2 had assisted breech deliveries. In one patient, caudal was administered for a Voorhees bag insertion, and in another a low

cervical cesarean section was performed entirely under caudal anesthesia.

In this series of 400 cases were 4 cardiacs, 2 patients with moderately advanced pulmonary tuberculosis, and 2 eclamptics.

RESULTS

Within the first 5 minutes after the anesthetic is administered, the outcries of the woman in the throes of labor are suddenly stilled, and the parturient, who only moments before had been writhing in pain, becomes quieted. Since the excitomotor reflex, due to pressure of the presenting part on the perineum, is abolished, the patient loses the urge to bear down; instead, she becomes mentally at ease and physically comforted. Yet the rhythmic uterine contractions continue painlessly, with the same frequency and duration as before, although, it is our impression, somewhat diminished in their intensity. The last-mentioned observation is not reliable, we admit, since the impression was obtained only by palpating the contracting uterus and observing its effect on the progress of labor. Several minutes after analgesia is obtained, anesthesia of the perineum develops. In tests for the loss of cutaneous sensation, which were made by grasping the skin with an Allis forceps, the development of anesthesia was consistently found to begin in the region of the anus and then spread fanwise upward toward the symphysis pubis, backward over the sacrum and gluteal regions, and laterally along the inner aspects of the thighs—the sum effect being a typical "saddle" anesthesia. Simultaneously, the musculature of the pelvic and perineal floors becomes completely relaxed. Even in primaparas, the lubricated examining hand can easily be admitted for such obstetrical manipulations as manual rotations, decompositions, and the like. Such relaxation greatly facilitates the application of forceps and reduces the incidence of vault tears. Sensation in and control of the lower limbs is unaffected. Caudal anesthesia has no effect whatsoever on the fetus. Furthermore, the third stage of labor is unaltered, as in only one instance was more than a simple Credé of the uterus necessary for the expression of the placenta. We believe, in fact, that the blood loss is less than that accompanying a delivery under ether anesthesia, since the relaxing effect of the ether on the myometrium is absent. The return of sensation occurs inversely to the direction in which it extended—beginning at the periphery of the saddle zone and advancing concentrically toward the anus. The postpartum period is unaltered.

In all but 13 of this series, the anesthetic was administered at complete cervical dilatation. In the first of these, it was given to a multipara at 3 centimeters' dilatation, to determine the effect on the progress. This was our first failure. In the second, it was administered at 6 centimeters' dilatation, with the anterior lip of the cervix impinged between the advancing head and the symphysis pubis. The edematous cervix was liberated and forceps were applied. In the third and fourth cases, primiparas, fetal distress became evident at 6 and 8 centimeters' dilatation, respectively. Manual dilatation was done and the infants were delivered with midforceps. The fifth case was a sextigravida, with an acute upper respiratory infection. The caudal block was done at 8 centimeters dilatation, and she was permitted to delivery spontaneously. In the sixth case, a primipara, low forceps were applied earlier because of increasing signs of maternal exhaustion. In the seventh case, labor was terminated at 8 centimeters dialatation because of a co-existing lobar pneumonia. In the eighth and ninth cases, multiparas, forceps were applied through an almost completely dilated cervix, because of heart disease; neither of these two had antepartum care; one was admitted in labor with auricular fibrillation, and the other, with mitral heart disease, gave a history of having been decompensated during the second trimester. In the tenth case, a primapara, progress in the first stage was arrested in midpelvis by an obstructing calcified vaginal cyst. In the eleventh case, the cervix was undilated. A Voorhees bag was inserted to institute labor, medical induction having failed. The twelfth and thirteenth cases were elective cesarean sections and naturally the cervices were not dilated at the time.

Obstetrical analgesia, morphine and scopolamine, was administered to only 110 of the 400 cases. The omission of a narcotic was purposeful, since competent and reliable co-operation of the patient was desired in so far as volunteering accurate information as to the subjective effects of the caudal block on uterine and perineal pain.

Complementary anesthesia, ether, was given to 22 of the patients. Eleven were the cases in which the caudal block had failed completely. Ten experienced "traction" pains during forceps delivery, necessitating ether for the delivery of the head only; the episiotomy repairs were done under the effects of the caudal block. In 1 case complementary ether anesthesia was required when it was found that the caudal block gave insufficient relaxation for an internal podalic version and extraction.

QUANTITY OF SOLUTION

In 10 of the patients, 20 cubic centimeters was injected; in 5 cases, 50 cubic centimeters was used; in 27 cases, 35 to 40 cubic centimeters administered; in 1 instance, only 10 cubic centimeters was given; in the remaining, 25 cubic centimeters was used. The patient who had received only 10 cubic centimeters experienced sufficient "traction" pain to require complementary ether. Generally speaking, for ordinary obstetrical procedures, no advantage was observed when either greater or lesser quantities than 25 cubic centimeters was injected.

ONSET OF ANESTHESIA

The shortest latent period between the time of administration of the anesthetic and the time when anesthesia became evident about the anal region was 2 minutes; the longest was 20 minutes; the average of the series was 7.4 minutes. Generally speaking, it was observed that approximately the same period of time was required for the complete extent of the anesthesia to develop from the time it first became evident, as had elapsed from the time the solution was injected to the time anesthesia was first noted.

DURATION OF ANESTHESIA

The longest period of anesthesia was 3 hours; the shortest, 36 minutes; the average for the series was 1 hour and 29 minutes.

AREA ANESTHETIZED

Consistently, the area over the sacrum and the gluteal regions, as well as the inner aspect of the thighs, was anesthetized, but the height to which the anesthesia rose on and above the vulva varied. Imagining the length of the vulva from the fourchette to the symphysis pubis being trisected into equal zones, it was found that when 25 cubic centimeters of metycaine was injected only the lowest (posterior) zone was affected in 1 case; only the two lower zones in 16 cases; and that the anesthesia extended up to and including the clitoris in 343 of the remainder. In 3 cases, anesthesia was observed to have extended from the level of the tenth dorsal spine to the toes; in 3 cases, it included the area from the level of the xyphoid to the knees.

That the quantity of solution injected has a definite relationship to the height to which the anesthesia rises on the anterior abdominal wall is evidenced by the fact that, except for 2 cases in which it did not ascend beyond the symphysis pubis, all 32 cases in which 35 cubic centimeters or more of solution was administered developed anesthesia to the level of the umbilicus or higher; in several cases, in fact, it rose to the level of the xyphoid. Therefore, we conclude that, with the larger quantities, the anesthetic solution dissects its way under pressure in the extradural space to bathe the nerves at higher levels in the spinal column.

Taking advantage of this phenomenon, which we have discovered only in the recent past, we have extended the use of caudal anesthesia in obstetrics to cesarean sections, and in the gynecological service we have adopted it for selected laparotomies.

RESULTS

We were able to classify our results as follows:

++++(4 plus): Anesthesia of the perineum. Loss of contraction pain.
+++ (3 plus): Anesthesia of the perineum. Patient aware of contraction pain.
++ (2 plus): Anesthesia of the perineum. Loss of contraction pain. Patient experienced pain when traction with forceps was applied.
o (o): Complete failure.

Guided by these criteria, the results could be grouped numerically as follows:

	Cases
++++ (4 plus):	348
+++ (3 plus):	31
++ (2 plus):	10
o (o):	11

Failures are usually due to inability to locate the sacral hiatus. Very obese women, in whom thick, soft tissue pads obscure the anatomical landmarks of the back and patients with deformities of the lower spine are, obviously, poor candidates for even an attempt at caudal block.

EFFECT ON VASOMOTOR SYSTEM

Realizing the occasional untoward effects of spinal anesthesia on the blood pressure, the influence of the epidural infiltration was closely watched. Sphygmomanometer and pulse readings were taken before the injection, during, and after, the delivery. Variations were inconsistent. In the greater number of cases, the blood pressure had not fluctuated more than 15 millimeters of mercury; in a few, the pressure had risen; in a few, a fall was observed. Other than the normal variations, i.e., the rise accompanying the pains and the expulsion efforts of the delivery, and the fall upon its termination, no remarkable influence of the metycaine on the blood pressure was noted. Similarly, no consistent abnormal influence of the caudal block on the maternal pulse was observed.

SIDE EFFECTS

Immediately after the injection of the anesthetic agent had been completed, 5 of the patients developed transitory episodes of disorientation accompanied by clonic convulsions, most marked in the upper extremities. The longest seizure lasted 2 minutes, following which, as with the others, labor was completed uneventfully. Five others became disoriented and apprehensive for several minutes after the administration of the drug. No tremors or convulsions accompanied their reaction. For want of a more satisfactory explanation, we surmise that these reactions were due to individual sensitivity to the drug. The untoward vasomotor, respiratory, and gastrointestinal symptoms and signs, such as tachycardia, palpitation, hyperpnea, pallor, nausea and vomiting, as reported by others, were not observed in any of our series. It is our deduction that such side effects may well be due to the epinephrine which the others had added to their anesthetic agent.

CONCLUSIONS

Caudal block offers a feasible and efficacious anesthesia for operative obstetrics. It permits the uterus to contract painlessly; it relaxes the pelvic floor and anesthetizes the perineum. It is harmless to both the parturient and her newborn. It permits the normal separation of the placenta and involution of the pelvic organs. All the untoward side effects of inhalation anesthesia are absent—there is no excitement stage, no nausea or vomiting, no danger of explosion. It lends itself well to an obstetrical service in which drop-ether, possibly administered by an untrained interne or nurse, is the only other available anesthesia. It can be used without fear in patients with pulmonary, cardiac, or renal complications.

The accompanying drawings are by Mr. Leo C. Massopust.

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PUTRID EMPYEMA

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In most discussions of suppurative pleuritis little or no distinction is made in the treatment recommended for various bacteriological types of pyogenic empyema. Only tuberculous empyema is considered as a distinct entity. Yet due to certain differences in the pathology of an anaerobic empyema from that of an aerobic infection of the pleural cavity, important modifications in the plan of treatment are necessary for the former group. Clinically it is easy to differentiate an aerobic from an anaerobic empyema in most instances. The common aerobic pleural infections yield purulent fluid which has no offensive odor. The pus in anaerobic pleural infections is usually very foul, and for this reason anaerobic empyema is also called putrid empyema.

The importance of certain fundamental principles in the treatment of aerobic empyema has been definitely established. The necessity of avoiding open thoracotomy in the early stages of a suppurative pleurisy has been stressed because it may lead to collapse of the lung and mediastinal displacement. After the suppurative pleuritis has been present for a sufficient length of time, the inflammatory reaction causes stabilization of the mediastinum and fixation of the lung, and open thoracotomy is then well tolerated. Observations on the thickness, specific gravity, or amount of sediment of the aspirated fluid have been used as clinical guides as to the time when open thoracotomy could be safely employed. Therefore, in general we regard the thickness of the pus as a criterion of the degree of mediastinal stability and pleural thickening. Although these observations on the pus are a very useful and valuable clinical guide in the treatment of aerobic empyema, the dictum to delay open thoracotomy until the pus is thick should not be applied to anaerobic empyema. Early open thoracotomy is indicated in anaerobic empyema regardless of the consistency of the purulent fluid. In putrid empyema the pus may remain thin for a long time. The marked toxicity of many of these patients, due to the type of pleural infection present, necessitates early drainage. The fact that the pus in anaerobic empyema continues to be thin for a considerable time in some cases does not mean that little pleural thickening is present or that the mediastinum fails to stabilize. *In anaerobic empyema the consistency of the pus is an unreliable guide as to when open thoracotomy may be performed with safety.* As the anaerobic pus causes marked toxicity, and as repeated aspiration of the foul fluid with a needle is very dangerous because of the frequency of severe thoracic wall infections, these cases must be treated somewhat differently than aerobic empyema. This does not mean that the same fundamental principles of treatment are not applicable to both aerobic and anaerobic empyema; the principle of avoiding mediastinal flutter and pulmonary collapse applies to all cases of empyema. In anaerobic pleural infections, however, the thickness of the pus and mediastinal stability are not closely correlated due to the pathology of putrid empyema. Neuhof and Hirshfeld (3) emphasized the importance of recognizing putrid empyema as a distinct type of pleural infection because of the special pathology and therapeutic problems involved. They recommended early surgical drainage by open thoracotomy as the preferred method of treatment.

During a period of 2 years (1939–1940) 23 cases of putrid empyema were treated on the thoracic surgery service of Kings County Hospital. This group does not include any cases of anaerobic empyema following surgical intervention in the thorax.

Besides the group of cases analyzed in this paper the authors have observed a considerable number of cases of putrid empyema in other clinics. The poor results obtained when thoracotomy was delayed prompted the present study and plan of therapy.

Age. The patients in our series ranged from 19 to 72 years of age. Nineteen of the 23 cases occurred in the age group from 30 to 70. The average age of the patients was 47 years. The condition was encountered most frequently in the sixth decade of life. Although there were no cases of putrid empyema in children in this series, the condition does occur in childhood. Neuhof and Hirshfeld (2) reported 17 cases of anaerobic pleuritis in a series of 184 cases of empyema in children. The therapy for children and adults is similar.

Sex. In our series 20 of the 23 cases, or 87 per cent, were males, and 3, or 13 per cent, of the cases were females.

ETIOLOGY

Putrid empyema is usually secondary to intrapulmonary disease. Bronchiectasis, pulmonary abscess, and suppurative pneumonia are the most common primary conditions. Anaerobic empyema may also result from perforation of the esophagus, mediastinitis, and penetrating wounds of the thorax, or follow surgical contamination of the pleural cavity during lobectomy, pneumonectomy, or drainage of a pulmonary abscess. A foul empyema may also be secondary to a subphrenic infection which has perforated the diaphragm; in these latter cases, however, a somewhat different group of bacteria are encountered.

The almost constant association of foul dental sepsis with putrid empyema secondary to intrapulmonary disease led one of us (E.J.G.) to associate with the late Dr. C. Coulter to study the bacteriology of the pyorrheal pockets and the material from the intrapulmonary lesion. In a small number of cases the same organism, a very virulent anaerobic haemotoxin-producing streptococcus, was isolated from both lesions. Dr. Coulter's untimely death interrupted this work; however, he believed that this organism acted as a singularly virulent factor in producing anaerobic intrathoracic suppuration.

In many cases of ruptured pulmonary abscess a putrid pyopneumothorax results due to a free communication between the empyema and the intrapulmonary abscess cavity and hence with the bronchial tree. The etiology of the pleural infection in this group is obvious. There is another group of cases in which no bronchopleural fistula is present. In this latter group the pleural infection is probably due to the rupture of a minute subpleural abscess, which is so small that no bronchial communication with the empyema cavity is established. The pleura is infected by a direct extension from a similar type of infection in the underlying lung. More or less extensive pneumonitis may be present. In a considerable percentage of these cases there is a history of bronchiectasis preceding the acute illness. In most instances in which such a history is lacking, the infection in the lung and secondarily in the pleural cavity is due to aspiration of infected secretions from the mouth and upper air passages.

A mixed bacterial flora is usually present in anaerobic empyema. Fusiform bacilli, spirochetes, and anaerobic streptococci are the most frequent findings. Other organisms, including aerobes, may also be present. Symbiosis seems to be an important factor in the action of these organisms. It has been shown experimentally by Smith that a combination of organisms is necessary to produce a foul-smelling abscess in mice.

In every case in our series in which anaerobic cultures were made, anaerobes were demonstrated to be present in the pus. Streptococci were the most frequently demonstrated organism, both on the aerobic and anaerobic cultures. Hemolytic streptococci were found more frequently than nonhemolytic streptococci in both the aerobic and anaerobic cultures. Staphylococcus aureus was also frequently present and often grew both aerobically and anaerobically. Fusiform bacilli were frequently demonstrated on direct smear of the pus and sometimes on culture. Spirilla, Staphylococcus albus, Bacillus proteus, Bacillus subtilis, pneumococci, bacilli of the colon group, and some unidentified bacteria were also found.

SYMPTOMATOLOGY

On the basis of their history, cases of putrid empyema may be divided into two groups. In the one group there is expectoration of foul sputum which indicates the presence of an anaerobic suppurative process. The sputum may come from an intrapulmonary focus, such as a pulmonary abscess or bronchiectasis, or from an anaerobic empyema with bronchopleural fistula. In the second group the foul sputum is absent and the symptoms may suggest an ordinary pneumonia rather than a suppurative process either in the lung or the pleural cavity.

The majority of cases of putrid empyema have a history of previous intrapulmonary infection. There may be a history of a chronic productive cough, and the sputum may be purulent and at times foul. These are mostly cases of chronic bronchiectasis or chronic pulmonary abscess. In other cases the history suggests an acute pulmonary abscess which then ruptures into the pleural cavity. The severity of the symptoms at the time the empyema develops depends chiefly on whether a localized or extensive empyema results. When the perforation of the pulmonary abscess is into a localized portion of the pleural cavity, there may be little change in the patient's symptoms. When an anaerobic abscess ruptures into the free pleural space, the symptoms may be very acute and the patient's condition becomes rapidly worse. In some instances the patient may no longer raise sputum due to drainage of the contents of the abscess into the pleural cavity.

In those cases of putrid empyema without a history of acute pulmonary suppuration, the symptoms suggest a pneumonia. The acute illness is usually characterized by malaise, fever, and pain in the chest. There may be a cough which is

dry or productive of mucoid sputum; sometimes cough is absent. Occasionally the sputum is rusty or frankly bloody.

A definite history of chronic cough preceding the acute illness was recorded in slightly over half of our patients. We feel, however, that if the history had been more carefully taken, a considerably larger percentage of patients would have been found to have had a cough before the acute illness. In some instances the cough was productive of purulent sputum, but only a few patients gave a history of foul expectoration in the past. Several patients had had previous attacks of pneumonia, and one patient had pneumonia repeatedly. In one instance the pulmonary disease dated back to a foreign body which had remained in the bronchus for several months before it was removed endoscopically 18 months prior to the development of the empyema.

DIAGNOSIS

When a putrid empyema is secondary to an acute pulmonary abscess, the diagnosis is usually not difficult if the intrapulmonary focus has suddenly ruptured into the free pleural space. More frequently, however, there is only an encapsulated empyema associated with the pulmonary abscess, and the diagnosis may be difficult to make. The change in physical signs and roentgen studies may indicate the presence of a secondary empyema. Sometimes the co-existing empyema is diagnosed only at the time of thoracotomy.

It is in the cases of putrid empyema without evident previous intrapulmonary suppuration and without foul sputum that the diagnosis is often delayed. At the time of onset of the acute illness a diagnosis of pneumonia is usually made. Certain atypical features may be noted. The sputum may not be rusty, and although a lobar pneumonia is frequently diagnosed, it may be found difficult to type the sputum. Early in the course of the illness the physical signs may suggest the presence of pleural fluid. Roentgenograms may reveal findings consistent with pneumonic consolidation or pleural effusion. The density is frequently interpreted as pulmonary consolidation when it is chiefly due to pleural fluid. The mediastinum is less likely to be displaced in anaerobic empyema than in aerobic empyema because previous pulmonary disease is frequent in the former group and tends to fix the mediastinum.

Most of the patients in our series gave a history of a rather sudden onset to the acute illness. Chest pain was complained of at some time in almost every case. Twenty of the 23 patients had a cough. In 13 cases the cough was productive, but only 5 patients had foul sputum. In each case of foul sputum there was either an associated pulmonary abscess of appreciable size or a bronchopleural fistula. Only 3 patients had bloody sputum.

A preliminary diagnosis of pneumonia was made in most of the cases. In 4 instances, a pulmonary abscess was diagnosed. Over half of the patients received one of the sulfonamide drugs before the diagnosis of empyema was made. These chemotherapeutic agents do not give the typical dramatic response in this type of infection. In fact the failure to respond to the sulfonamides is a point in the differentiation of the atypical pneumonia associated with a foul empyema from the typical pneumococcus pneumonia. About half of the patients were regarded to be critically ill at the time of admission to the hospital.

The diagnosis of putrid empyema is definitely established by the aspiration of foul pus or foul air from the pleural cavity. Due to the previous intrapulmonary disease causing pleural adhesions, the empyema may be somewhat loculated. We have seen considerable delay in making the diagnosis in several cases due to an anterior location of the empyema. Low aspiration should be avoided because the diaphragm may be elevated as a result of the previous intrapulmonary disease. If the needle traverses the diaphragm, subphrenic infection may result. A spreading subphrenic infection due to this cause was present in one of our cases and it has also been observed by Neuhof and Hirshfeld (3). A similar complication in aerobic empyema is very unusual. In 2 instances in which the diagnosis of a putrid empyema was made very early, the aspirated fluid was clear and serous, but the overlying air was foul. The odor is therefore present early.

Smears of the aspirated fluid should always be done; usually a variety of organisms will be found. Special examination with the darkfield microscope should be done for spirochetes. Aerobic and anaerobic cultures should be planted. Improper and incomplete examinations of the pus may result in a failure to identify the anaerobic organisms, and hence the occasional laboratory report that this foul fluid is sterile! One does not need to await the report of the culture of the pus, however, to know that immediate surgical intervention is indicated. If tuberculosis were also present, open thoracotomy would still be indicated except in rare instances.

TREATMENT

The importance of immediate treatment in cases in which an anaerobic pulmonary abscess

has ruptured into the free pleural space has been recognized for some time. These patients are best treated by open thoracotomy.

In an anaerobic empyema without clinically demonstrable pulmonary abscess and without bronchopleural fistula, there is usually unwarranted delay in instituting proper therapy. Open thoracotomy with rib resection should be performed as soon as the diagnosis of putrid empyema is confirmed by aspiration. There may be a rare case in which it may be advantageous to delay the thoracotomy for a day or two because of a massive fluid accumulation with mediastinal displacement. In such an instance an incision under local anesthesia should be made through the skin, subcutaneous tissues, and deep muscles of the thorax down to the ribs and intercostal muscles at the site of the exploratory aspiration. This incision should be made within a few hours of the first aspiration. Further aspirations are done through the open wound, which is packed with zinc peroxide gauze. Of course some cases of anaerobic empyema may be aspirated repeatedly without a thoracic wall infection developing, but the incidence of infections following thoracentesis is quite high and, when once developed, the thoracic wall phlegmon is of such severity that aside from intrapulmonary disease it is the most important factor in the mortality in these cases. This is entirely different from the situation in aerobic empyemas, in which, with proper technique, infection in the thoracic wall is relatively uncommon following thoracentesis, and, if infection develops, it can usually be easily controlled by simple measures.

The reasons for the serious and frequent thoracic wall infections with anaerobic empyema are several. The pus is often watery in character and, therefore, can leak through a small needle track. Secondly, we are dealing with anaerobic organisms which are likely to gain a foothold in a puncture wound in which conditions are favorable for their growth. The ease with which appreciable amounts of this infected fluid leak through the needle track in the intercostal muscles has been convincingly shown at operation when the pleural cavity is needled after the chest wall incision has been carried down to the ribs. The fact that gross leakage of the pus occurs and that it gravitates downward from the puncture site beneath the deep thoracic muscles is shown by the location of the infection in the thoracic wall, which may extend almost entirely in a downward direction from the aspiration site.

Surgical drainage of thoracic wall infections following aspiration of an anaerobic empyema may be delayed because a cellulitis rather than an abscess is diagnosed. The pus usually collects just outside the ribs and beneath the thoracic muscles. Therefore tenderness and some swelling may be the only indication of chest wall infection. Redness of the skin may be absent. Fluctuation is usually not demonstrable because of the deep site of the purulent collection. For these reasons several days may elapse before the chest wall infection is considered ready for incision and drainage By this time extensive gangrenous infection of the deep tissues of the thoracic wall may be present. We have seen extensive necrosis of the tissues within a day of a thoracentesis which yielded thin foul pus. The periosteum of ribs and scapula may be destroyed with resultant osteomyelitis.

As mentioned previously, with very few exceptions, a thoracotomy with rib resection is performed under local anesthesia as soon as the diagnosis is made. The patient is placed in such a position on the operating table as not to flood his bronchial tree with pus in those cases with free bronchopleural communication. In a considerable number of cases the only safe position is with the patient sitting upright. The surgeon himself should supervise the placing of the patient on the operating table so the proper position for that particular patient may be chosen.

A long incision is made through the area of aspiration. Care is taken not to undercut the muscles. A rather long segment of one or occasionally more ribs is removed. The empyema cavity is opened cautiously because of the possibility of pulmonary collapse. Although the mediastinum is usually stable, precautions must be taken in the event that this should not be the case. If there is sucking of the wound associated with mediastinal shift, the patient should be promptly rolled over onto a large wet dressing as this will markedly diminish the flow of air through the opening. Although we have always been prepared to do this, so far we have not found it necessary. The pus is removed by suction and the presence or absence of bronchial fistula noted. Occasionally the opening into a pulmonary abscess is enlarged. Large rubber tube drains are inserted. It is imperative that no sutures whatsoever are inserted in the thoracic wall. A single suture inserted for the purpose of anchoring a drainage tube may result in a spreading thoracic wall infection of a serious nature. Adhesive strapping may be employed instead. The edges of the wound should not be strapped, as the large opening is a great asset. The chest wall wound is packed with gauze soaked in zinc peroxide. In small empyema

cavities without bronchopleural fistula, zinc peroxide has also been placed in the pleural cavity. Zinc peroxide is of great value in the treatment of anaerobic thoracic infections (1).

Twenty-two of the 23 patients in this series were treated by thoracotomy with rib resection and open tube drainage. Two of the patients had an incision made in the chest wall down to the ribs a few days before the open thoracotomy was done. In one case the pleural cavity was not drained surgically because this patient died in diabetic acidosis a few hours after a phlegmon of the chest wall was drained.

Because of previous unsatisfactory results when open thoracotomy was delayed in cases of foul empyema, most of the patients in this series were treated by rib resection shortly after the diagnosis was made by thoracentesis. Half of the patients were operated upon within 24 hours of the first aspiration. The delay in most of the other cases was due to the fact that the patient was not immediately transferred to the surgical service. Eighteen of the 23 patients had only a single thoracentesis before thoracotomy. Two patients were aspirated more than twice; both of these patients died.

At the time of open thoracotomy the pus was thin in 9 cases and thick in 14 cases. The lung was partly adherent to the lateral thoracic wall in 17 of the 23 cases. In the remaining cases the empyema was extensive. In 8 of the 9 cases in which the pus was thin at the time of thoracotomy, the lung was prevented from complete collapse by adhesions to the thoracic wall. In the single case in which the pus was thin and the lung was not adherent when thoracotomy was performed, the lung re-expanded well after operation. Therefore, in this series of cases the drainage of putrid empyema when the pus was thin did not result in any difficulty with mediastinal shift or late re-expansion of the lung.

Chest wall infections developed before thoracotomy in 4 of the 23 cases, or an incidence of 17 per cent. This does not give a true picture of the danger of this complication in putrid empyema, however, because most of the cases in this series had a thoracotomy performed shortly after a single aspiration. Three of the four thoracic wall infections developed after a single aspiration and were clinically manifest within 24 hours of the only thoracentesis. The other case had three aspirations performed. Two of the 4 patients with phlegmons of the thoracic wall died. Both of these fatal cases also had diabetes mellitus, and the chest wall was not drained until 4 days after the thoracentesis. In the 2 cases with chest wall infection that recovered, the thoracic wall was drained the day following the chest aspiration. In 3 of the 4 cases of phlegmon the fluid aspirated from the pleural space was thin. In the single case with thick pus, many fusiform bacilli and other anaerobes were found in the purulent material.

Various complicating conditions were present in addition to the pulmonary and pleural infection. Two patients had diabetes mellitus. Four patients were cardiacs, and 2 of these were decompensated before thoracotomy. One patient had a toxic hepatitis and acute tonsillitis with cervical adenitis. Several had general arteriosclerosis and chronic nephritis.

POSTOPERATIVE COURSE

With proper early operation the prognosis is good as far as the pleural infection is concerned. The foul odor may be gone within 24 hours. The patient may show remarkable improvement. If there is extensive intrapulmonary suppuration, this will be the most important factor in prognosis. Oxygen therapy should be used freely.

The chest wall wound often has a necrotic appearance unless zinc peroxide packing is inserted into the thoracic wall wound. This agent is most effective in these anaerobic infections. Care should be taken to prevent the drainage opening from contracting down too quickly. The retention of a very small amount of pus may cause quite a febrile reaction. If a bronchopleural fistula is present, drainage should be prolonged.

The use of sulfonamides seems to be of benefit in some cases. We have employed chemotherapy in several cases in which there was a febrile course after operation apparently due to residual pulmonary infection. Before ascribing the fever to intrapulmonary disease, one must ascertain that the pleural drainage is entirely satisfactory. At the time of drainage of the empyema it may be difficult to evaluate the extent of the intrapulmonary suppuration. If putrid sputum persists after operation, it should be ascertained whether this comes from an undrained pleural pocket with bronchial communication or from the lung. Some mucoid sputum may persist for a considerable length of time.

Painful swollen joints have been present in several of our cases in the postoperative period. In 2 instances the joint pains were associated with fever for several weeks, but the onset of these symptoms was more than a month after adequate drainage of the empyema.

Most of the patients continued to be febrile for considerable periods of time after the empyema

was drained. This was thought to be chiefly due to the slow subsidence of the intrapulmonary infection. Less than half of the patients became afebrile within 3 weeks of thoracotomy. Several continued to be febrile for almost a month, and in 4 cases the temperature became normal only from 6 to 7 weeks after the empyema was drained. In view of the slow subsidence of the intrapulmonary infection, and because we did not wish to discharge these patients while the empyema cavity was of sufficient size to require a drainage tube, the period of hospitalization was prolonged. Most of the patients remained in the hospital for a period of 2 to 4 months from the time of admission.

RESULTS

Three of the 23 patients died, giving a mortality of 13 per cent. One patient died as a result of multiple pulmonary abscesses and an extensive phlegmon of the chest wall which followed a thoracentesis done 4 days before the thoracotomy. This same patient also had an anaerobic subphrenic abscess on the same side and diabetes mellitus. Death was chiefly due to the extensive intrapulmonary suppuration. The second death occurred as a result of diabetic acidosis which was not controlled because of a chest wall phlegmon and an undrained anaerobic empyema. In this case we feel that early drainage of the empyema before the chest wall became infected might have resulted in a successful outcome. The third death was also in a case in which thoracotomy was delayed, and there was an undrained pulmonary abscess.

All 20 patients who recovered obliterated the empyema cavity after thoracotomy and their wounds healed. None required any further surgical procedures as far as the empyema was concerned. Some of the patients continued to have chronic cough and sputum due to the persisting intrapulmonary disease.

CONCLUSIONS

1. Putrid empyema should be differentiated from aerobic empyema.

2. Thoracentesis in cases of putrid empyema is associated with considerable danger of a serious thoracic wall infection.

3. Early open thoracotomy is the treatment of choice in putrid empyema.

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MAMMARY CARCINOMA

A Review of 2,636 Cases

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TO augment the already voluminous and frequently repetitive literature on mammary carcinoma is an act which one should contemplate with considerable misgiving. More articles have been published on the subject of carcinoma of the breast than on any other single regional form of cancer. A greater number of radical surgical procedures have been performed for mammary cancer than for all types of malignant lesions of the entire gastro-intestinal tract (24). The accessibility of the breast, its predilection toward the development of both benign and malignant lesions, and the complex pattern of its hormonal control have made its problems a matter of interest to investigators in widely separated fields. Nevertheless, the accumulation of knowledge concerning mammary cancer has not produced any commensurate degree of agreement among research workers or clinicians as to its problems, either epidemiological, etiological, or therapeutic.

The present study is based on a review of 2,636 abstract clinical records of carcinoma of the breast in the cancer archives of the American College of Surgeons. Although the College established the cancer archives primarily as a repository for the abstract records of "cured" cancer cases, the material reported here includes 1,511 5 year "cures" and 1,125 cases in whom recurrences or metastases developed within the 5 year period. Contributed by many institutions and individuals in the United States and Canada during the past decade, this material is obviously not susceptible of analysis by methods used in the review of consecutive cases in a single institution. Any attempt to evaluate the therapeutic methods used in such a collected series would be particularly fallacious for this and other reasons meriting wider recognition.

The number of cases included in this study is sufficiently large to make possible an evaluation of certain factors of interest in the genesis, prognosis, and management of mammary carcinoma. The factors studied are seven in number: age, family history of cancer, childbearing, lactation, known duration of tumor, stage of disease at treatment, and the survival of "cured" cases after the 5 year period. All of the cases included in this study are recorded as having had histological confirmation of some form of mammary carcinoma. Instances of sarcoma of the breast, and of carcinoma in the male breast, have been excluded. "Five year cure" cases are arbitrarily defined as those in whom a minimum period of 60 months has elapsed following treatment without clinical evidence of recurrence. Practically all of the records studied were submitted on the abstract cancer record form recommended by the cancer committee of the American College of Surgeons, the uniformity of which greatly facilitates this type of study. Unfortunately, as shown in Table I, the variability of detail in which the forms were completed proportionately determined the number of cases available for analysis of the several factors studied.

AGE

In Figure 1 is presented the comparative age distribution of 1,486 5 year cures and 1,045 recurrent[1] cases, and, drawn to scale, the estimated current cases of mammary cancer by age groups in the white female population of the United States. Table II shows the detailed figures from which this graph was constructed.

The number of cases up to the age of 35 is not sufficiently large to be of real significance. There is, however, legitimate cause for interest in the 13 cases in which patients were under the age of 25 years. Ten of this group were 5 year cures and only 3 were recurrent cases. Most noteworthy is the slight but consistent percentage excess of 5 year cures over recurrent cases in the age period from 36 to 50 years. Past the age of 50, the percentage of recurrent cases is greater, and this unfavorable balance carries through to the most elderly group of 70 and over. The curves, both for the 5 year cures and the recurrent cases, roughly parallel those for the estimated current cases in the general population indicating that age is not an important prognostic factor in cancer of the breast.

Such a conclusion is in sharp conflict with a current attitude recently expressed by Pack and Liv-

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[1]The expression "recurrent cases" is used throughout to designate cases in which recurrence or metastases appeared before the 5 year post-treatment period elapsed.

Fig. 1. Percentage age distribution of 1,486 5 year cures and 1,045 recurrent cases.

ingston that cancer of the breast is a "much more menacing disease in young women than in mid-life or old age". So general has this impression become that there seems to be an attitude in many clinics of adopting less aggressive therapeutic measures in patients under 40 years of age. The rapid course of inflammatory carcinoma of the breast, more common in younger women, and the gravity of mammary carcinoma occurring in the pregnant or lactating patient undoubtedly lend additional weight to this credence. One also has the impression that the statistics from specialized cancer institutions are weighted by the proportion of referred problem cases among younger women.

A number of studies of end-results in general institutions have demonstrated that age has little bearing on prognosis (5, 10, 12, 18, 23, 28, 29). The balance of evidence, in fact, indicates a more favorable outcome for patients in the fourth than in the sixth decade. Evans and Leucutia, in a study of 1,200 cases, after corrections had been made for natural factors of longevity, found a distinct excess of 5 and 10 year cures in the group under 40 years of age over those in the sixth decade. Lewis and Rienhoff studied the 10 year end-results of surgical treatment at the Johns Hopkins Hospital from 1889 to 1931, and concluded that no essential variation could be shown for the age groups from 30 to 70 years. An analysis of percentage 5 year "survivals" by age groups of 3,740 cases, reported by Harrington in 1935, also demonstrates the less favorable results of treatment in women of 55 to 64 years of age.

The evidence presented here strongly supports the contention that the best results in the treatment of breast cancer are obtained between the ages of 35 and 50. The thesis that an especial virulence exists for mammary carcinoma in the young is not verified.

TABLE I.—CASES AVAILABLE FOR ANALYSIS OF SEVEN FACTORS IN 2,636 RECORDS OF MAMMARY CARCINOMA

Factor	Number of records with adequate data
Age	2,531
Family history of cancer	1,278
Fertility	1,817
Lactation	1,146
Duration of tumor	1,945
Stage of disease (5 year cures)	1,511
Survival of cured cases	1,553

HEREDITY

Information concerning the hereditary background of cancer patients gleaned from ordinary

TABLE II.—AGE IN 2,531 CASES

Age group	Five year cures		Recurrent cases		Current cases
	No. cases	Per cent	No. cases	Per cent	Per cent
Less than 25	10	0.7	3	0.3	
26 to 30	26	1.7	34	3.3	0.8*
31 to 35	77	5.2	65	6.2	2.6*
36 to 40	152	10.2	80	7.8	6.7
41 to 45	253	17.0	158	15.0	10.8
46 to 50	280	18.9	166	15.9	14.9
51 to 60	397	26.7	293	28.0	34.0
61 to 70	237	16.0	178	17.0	30.2
71 or more	54	3.6	68	6.5	
	1,486	100.0	1,045	100.0	100.0

*Interpolated.

clinical records is probably of little value. The "false negative" history is the most frequent pitfall, for to elicit accurate information may demand searching inquisition. For this reason, only those records showing a definite negative statement under the heading of "Family History of Cancer" were accepted at face value, while those bearing "No", "o", or other symbols of negation (or omission) were generally excluded. As depicted in Figure 2, 1,021 of 1,278 records indicated an absence of cancer in the immediate family—80.0 per cent—while there were 84 instances—6.5 per cent—of mammary cancer and 173—13.5 per cent—of cancer elsewhere recorded as positive family history. These figures fail to approach the results obtained by Waaler, in Norway, and Wassink, in Holland. Cramer, in a recent review of the work of these investigators, reported that 31 per cent of Wassink's 1,660 patients gave a history of cancer in other members of the family.

Of more importance was the fact that the incidence of breast cancer in the female cancerous relatives in Wassink's series was remarkably high, amounting to more than 50 per cent, in contrast to the general prevalence of only 10 per cent of mammary cancer in cancerous Dutch females. In this respect, the present series of cases shows that 31.1 per cent of all cancerous relatives had breast cancer, while deaths from this form of cancer account for only 11.1 per cent of all cancer deaths in the United States. Thus, there is revealed, by what the epidemiologist would term extremely casual history taking, an impressive preponderance of breast cancer in the cancerous relatives of American women with mammary cancer. It seems apparent that, if it were possible to apply the same analytical criteria, the excess of breast cancer in the female cancerous relatives would approach that determined by Wassink's study. An analysis by Martynova of the family history of 201 Russian women showed, that among the female relatives, mammary cancer was more frequent at all ages than in the control population. There are also a number of instances of the development of breast cancer in identical twins (27), and Macklin has presented convincing evidence of the heredity of human breast cancer.

Evidence thus accumulates that, although there may be only a slight excess of a positive family history of cancer in all cases of mammary cancer, there is nevertheless a distinct excess of breast cancer among their cancerous relatives. It is apparent that in a certain proportion—20 to 30 per cent—of cases there is an inherited susceptibility, and that in the relatives of these women the incidence of breast cancer is at least three times greater than in the general population.

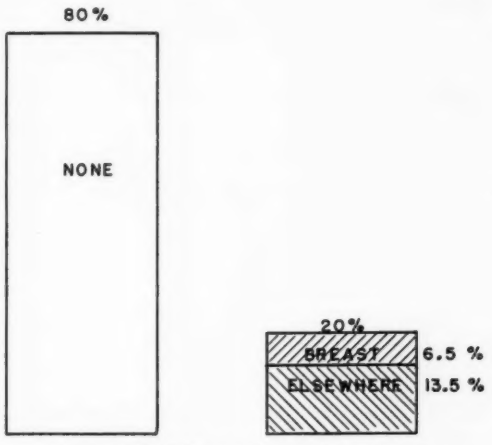

Fig. 2. Family history of cancer in 1,278 cases.

FERTILITY

Of 1,817 cases in which data were available concerning childbearing, 40.8 per cent were nulliparous and 59.2 per cent had borne one or more children. On the basis of fertility prevailing among white females in the United States in 1937, Dublin estimates that approximately 66⅔ per cent of white women in the United States bear children. There is thus an appreciable excess in nulliparous women in this series of breast cancer cases, 40.8 per cent, compared to the general population, 33.3 per cent. This finding is in agreement with the results of a number of careful studies (Wainright, Kaplan, Hoffman). Herring in this country and Lane-Claypon in England, have demonstrated a constant excess of mammary cancer among single women of all ages.

In the 1,075 women who had borne children, the number of viable children averaged 3.0 per mother, compared to an estimated average in the general population of 2.75 (Dublin). There was essentially no difference in the number of children per mother between the 895 5 year cures (average 2.9 children) and 922 recurrent cases (average 3.1 children). Of the 5 year cures, 44.6 per cent were nulliparae, while 37.1 per cent of the recurrent group had not borne children.

Although these results confirm the results of other statistical studies indicating that nulliparae are more prone to develop breast cancer than those bearing children, there is also evidence that once developed the prognosis is as good or even better for the nulliparous woman. Further, the

TABLE III.—FERTILITY IN 1,817 CASES OF MAMMARY CARCINOMA

	5 year cures	Recurrent cases
Nulliparae	400	342
No. children		
1	134	158
2	145	123
3	79	108
4	53	64
5	30	56
6	21	20
7	10	21
8	6	15
9	7	3
10	4	4
11	1	3
12	4	4
13	0	0
14	0	1
15	1	0
	895	922

number of children borne seems to have little or no influence in prognosis. These conclusions are drawn from the data presented in Table III.

LACTATION

Information concerning the functional activity of the breast was available in only 1,146 of the 2,636 records reviewed. Seven hundred and forty-two, 64.8 per cent, of these patients were nulliparous, but this figure is heavily weighted by the paucity of information in the abstract records concerning lactation in parous women. In only 404 records of childbearing women was there any approach to satisfactory information concerning their lactation. In 234 cases, the statement "normal" lactation appeared, and such statements were accepted at face value. It is more than probable, however, that careful questioning will disclose many abnormalities of lactation in women who maintain uncertain recollections of "normal" lactation (1). One hundred and forty-two of these 404 parous patients either had failed entirely to suckle, or during lactation had suffered such aberrations as "caked" breasts, abscess, and puerperal mastitis. Twenty-eight additional patients had nursed less than 3 months after one or more deliveries, compared to the 6 month period of lactation generally accepted as desirable. In practically all instances these abnormalities of lactation affected the breast which subsequently became the site of carcinoma, and in a considerable number the cancerous breast alone had been afflicted by inflammatory disease during lactation.

Using as a standard Wainright's figure that 20 per cent of American women in a control series had not lactated, in Figure 3 is charted the lactation history of this group of cases. Setting aside the 742 nulliparous cases, in 170, or 42 per cent of 404 parous women with breast cancer, the breast had failed properly to perform its physiological function of lactation.

Failure of normal lactation as a factor in the genesis of mammary cancer is a thesis which has received complementary verification from a number of clinical and experimental studies in recent years. Adair and Bagg (1), in a study of 200 cases, found only 8 per cent with accurate histories of normal lactation. Wainright found failure of lactation in 40 per cent of 637 patients, compared to only 20 per cent in 541 control cases. Lee reported that 31 per cent of 156 breast cancer cases had never lactated, without mention of abnormalities in lactation. In a tribe of African aborigines whose women habitually nurse their children for 2 to 3 years, Ellis found that mammary cancer was a rare disease.

Notable experimental evidence on this subject has been adduced by Bagg and his co-workers. Bagg's "functional test" in mice consists of rapid breeding of females coupled with prevention of suckling by withdrawal of the litters as early as possible after birth. By this means strains of inbred mice with low spontaneous incidence of mammary cancer have developed a greatly increased ratio of such tumors. In C 57 strain of mice which apparently had not developed a mammary tumor in 10 years of inbreeding, the functional test produced mammary tumors in 15 per cent of the animals subjected to this form of physiological stress. Bagg has further increased the incidence of mammary carcinoma in animals by ligation of the terminal ducts. The consequent stasis and ductal distention led to changes in the ductal epithelium which eventually gave rise to infiltrating carcinomas.

Such experimental and clinical evidence as has been presented makes possible the statement that failure of the breast to perform properly its physiological function is the most consistent apparent factor in the genesis of human mammary carcinoma. Whether the actual etiological factor is mechanical, due to distention of ducts and retention of secretion (19), or chemical, originating in retained products of lactation or in repeated hormonal stimulation, is beyond the scope of this discussion. Such analyses as are reported here and elsewhere, notably by Adair (1), may well lead one to regard normal lactation as a measure of prophylaxis against carcinoma of the breast of which obstetricians and pediatricians should be cognizant. There is a well recognized tendency, particularly among urban women, to shirk the

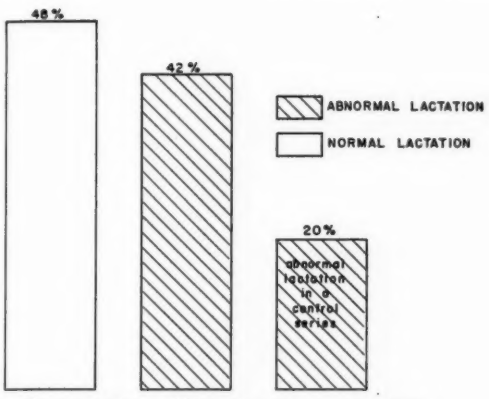

Fig. 3. Lactation history in 404 parous patients.

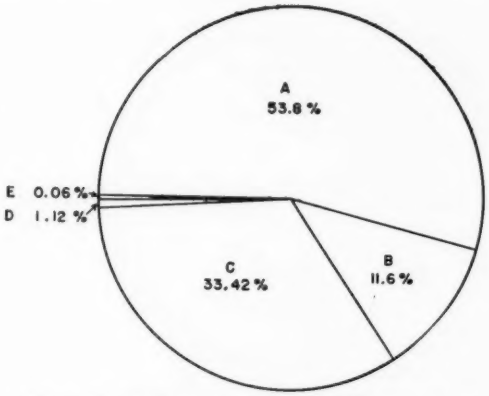

Fig. 4. Stage of disease at treatment in 1,511 5 year cures.

duty of breast feeding, and the frequency with which this practice is condoned and even recommended by physicians is to be deplored. It is entirely possible that the steadily increasing incidence of breast carcinoma in "civilized" women is in large measure due to complete or partial failure of lactation.

KNOWN DURATION OF TUMOR

In Figure 4 is graphically shown the known duration of the breast tumor from first recognition by the patient to treatment in 938 five year cures and 1,007 recurrent cases. The importance of early treatment is well illustrated in the sharp decline in the number of cases amongst the 5 year cures treated from 1 to 11 months after recognition of the tumor. Over the same period of increasing delay, the number of recurrent cases is generally though not consistently greater than that of 5 year cures. It is, however, the institution of treatment within the first 2 months that apparently produces the most appreciable increment in 5 year cures. With a delay of 12 months and over, both groups again show a sharp increase, with the recurrent cases in excess. The appreciable proportion of 5 year cures, 24.8 per cent, treated more than 1 year after the recognition of the tumor probably has a twofold explanation. Most obvious is the fact that the majority of these cases represent the indolent, slowly growing breast carcinomas of low degree malignancy which metastasize late, or occurring in hosts whose desmoplastic reaction to the tumor is intense. More debatable is the concept that some of these carcinomas arose in pre-existing benign lesions of the breast as suggested by the presence of tumors for periods as long as 5 years among the cured cases.

In those patients treated within 12 months after recognition of the tumor, the average period of delay was 3.08 months for the 5 year cures and 4.5 months for the recurrent cases. Of the 5 year cures, 44.6 per cent were treated within 3 months of recognition of the tumor, while 34.2 per cent of the recurrent cases were treated with equal promptness. Treatment was instituted more than 1 year after the tumor was noted in 24.8 per cent of the 5 year cures and 33.3 per cent of the recurrent cases. Thus there is a definite inverse relation between delay in treatment and chance of cure, though not as pronounced as one might expect.

Otherwise stated, 44.6 per cent of the 5 year cures were treated within 3 months, and 28.5 per cent 12 months or more after recognition of the tumor. Thus 73.1 per cent of all of the 5 year cures were treated either very early or very late, lending point to the natural division of breast cancer into 2 general groups: those which metastasize early and those which remain a localized disease for long periods of time. Recognizing in addition the fact that in a certain proportion of the cured patients treated early the tumors are of the slow growing type, one is confronted with the conclusion that in spite of the importance of early treatment in eradicating certain early lesions, end-results are determined more by natural selection than by early treatment. In general terms, this analysis indicates that of every 4 instances of 5 year cures of carcinoma of the breast, 2 are treated within 3 months, 1 from 9 to 12 months, and 1 more than 1 year after recognition by the patient.

FIVE YEAR "CURE" CASES

Stage of disease at treatment. The stage of the disease at the time of treatment in the 1,511 cases

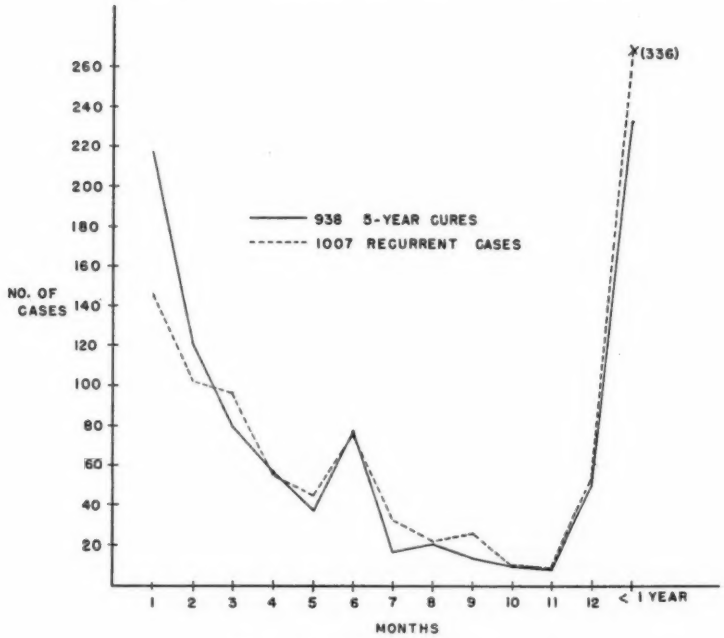

Fig. 5. Known duration of tumor.

of 5 year cures is shown in Figure 5. The classification used is that recommended by the cancer committee of the American College of Surgeons:

Stage A. Disease limited to breast.

Stage B. Questionable involvement of axillary nodes.

Stage C. Axillary nodes involved.

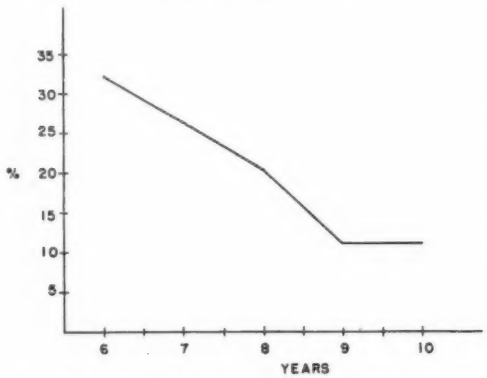

Fig. 6. Percentage distribution of 869 cases, 6 to 10 year cures.

Stage D. Supraclavicular nodes involved.

Stage E. Remote metastases present.

In this study, only those cases in which there had been microscopic confirmation of axillary node metastases were classified as Stage C. In 175 cases, 11.6 per cent, the records failed to provide adequate information on this point, and in view of the known inaccuracy in clinical judgment as to the presence or absence of axillary involvement (11), these cases were designated as Stage B.

The feature of interest in these figures is that 33.4 per cent of this large number of 5 year cures were histologically proved to be Stage C cases, a fact of the greatest clinical importance. Further, a majority of the cures classed as Stage B were those in which the presence of clinically positive axillary nodes was recorded but in which the microscopic confirmation was lacking. If one accepts Greenough's statistics that 90 per cent of the clinical Stage C cases are confirmed by the pathologist as such, then the proportion of Stage C cases in this cured group will approach 40 per cent. One series has been reported in which 50 per cent of 5 year survivals were Stage C cases (21). The inference is plain that to deny patients with operable growths the chance of radical treat-

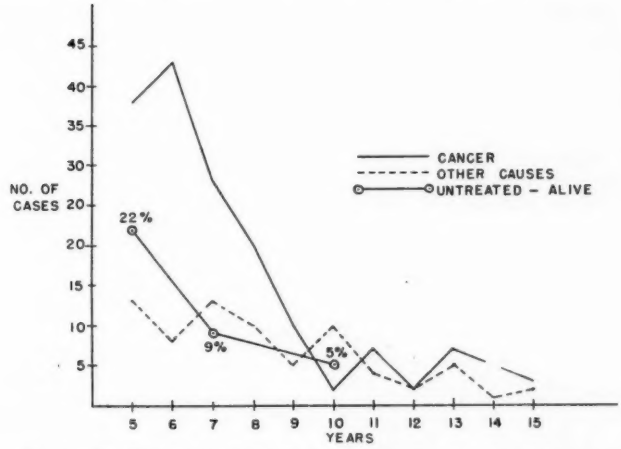

Fig. 7. Deaths from cancer and other causes after 5 years, 238 cases.

ment because of the presence of axillary metastases is therapeutic defeatism at its worst.

In general terms, it seems evident that of every ten 5 year cures, not more than 6 are Stage A at the time of treatment, usually the other 4 are Stage C, and very occasional patients will survive 5 years or more without recurrence when the disease has involved the supraclavicular nodes. This is not to imply that all patients in the Stage C group should be regarded as candidates for radical mastectomy, for their therapeutic management demands the utmost nicety of clinical judgment, based on a number of factors beyond axillary involvement *per se*. In fact, there are criteria of operability within the Stage C group, and many cases in this series are examples of the failure properly to apply such criteria. The point, however, must be made, that almost 40 per cent of 5 year cures will accrue from the proper management of Stage C cases, and consistent therapeutic indolence in these cases will result in the loss of 4 of every possible ten 5 year cures.

Survival. For the purposes of this study, a 5 year post-treatment period free from recurrence or metastasis has been used as a criterion of cure. There are certain forms of cancer with a predilection toward delayed recurrence so notable as to make the arbitrary 5 year period a poor gauge of therapeutic success. Basing his opinion upon a follow-up study of 167 cases, Bartlett concluded that "what happens after the fifth year is relatively unimportant," stating that only 1 patient died in the second 5 years. There is no small amount of evidence opposing this conception. Ducuing reported a progressive decrease in survivors from 8 per cent at the end of 5 years to 2.2 per cent in the thirteenth year. From the fifth to the fourteenth years Lewis and Rienhoff followed 322 cases, the survivors decreasing from 30.9 per cent to 8.7 per cent, the maximum loss occurring by the ninth year. Matthews made a 10 year follow-up study and concluded that a patient surviving the first 5 years had a 62.5 per cent chance of living 10 years, and that deaths between 5 and 10 years were mainly from cancer rather than from intercurrent disease. Survivors in Perry's series of 653 cases decreased from 28 per cent at 5 years to 16 per cent at 14 years. In 419 cases of recurrence reported by Pfahler and Vastine, 7 per cent appeared more than 5 years after treatment. Breast cancer has recurred more than 30 years after treatment.

In this series, 1,207 cases were reported at a time when they had been free of disease for 6 or more years, and of these 869 were 6 to 10 year survivors, 264 were 10 to 15 year survivors, and 74 for more than 15 years. The curve of survival for the 869 cases of 6 to 10 year survivors is shown in Figure 6. In Figure 7, plotted against Daland's statistics of survival in 100 untreated patients, are the mortality curves for 238 cases in which the time and cause of death is known, for those dying both of recurrence and intercurrent disease. It is evident from these graphs that the number of reported survivors and the deaths from cancer, both in treated and untreated patients, level off after the ninth year. As a true gauge of end-results, therefore, the 5 year yardstick is best replaced by one in which curative achievements are measured on the basis of 9 or 10 year statistics.

SUMMARY

The records of 2,636 cases of mammary carcinoma, 1,511 5 year cures and 1,125 recurrent cases, have been reviewed. Comparative statistics are presented for the factors of age, childbearing, and the known duration of tumor. Collective data concerning the influence of heredity and lactation in the genesis of the disease are analyzed. The stage of disease at treatment and the survival period of the 5 year cures are separately presented.

CONCLUSIONS

The age of patients with mammary carcinoma does not have the prognostic significance with which it is commonly accredited. Excluding the cases of "inflammatory" carcinoma and those occurring in gravid and puerperal women, more common in the young, carcinoma of the breast at any early age merits as radical an approach with as much chance of cure as in older women. The best results are obtained in those patients who are 35 to 50 years of age, and the least favorable in the decade from 50 to 60.

There is evidence of an inherited susceptibility to cancer in approximately 20 per cent of this series, but among the relatives of those women having an hereditary background of cancer there is an excess of breast cancer at least 3 times greater than in the general population.

Nulliparae are more prone to develop cancer of the breast than women who have had children, but once developed the prognosis is as good, or perhaps better, for the nulliparous woman. The number of children borne by parous women has little or no influence on prognosis.

The most consistent apparent factor in the genesis of mammary cancer is the failure of the breast to perform its expected physiological function. A full period of lactation in childbearing women seems to offer a degree of protection against subsequent development of breast cancer.

Early treatment is of utmost importance in the cure of certain early lesions predestined otherwise to undergo rapid growth and early dissemination, but in general end-results are determined more by natural selection than by early treatment. Tumors of long duration in themselves are no contraindication to radical treatment, for 25 per cent of the 5 year cures here recorded were treated more than 1 year after recognition of the tumor.

To deny patients with otherwise operable neoplasms the chance of radical treatment because of the presence of axillary node metastases is to face the possible loss of 40 per cent of attainable 5 year cures. Criteria of operability exist within Stage C (II) cases, requiring consideration of combined methods of therapy.

The 5 year post-treatment period as an arbitrary standard for the evaluation of therapeutic measures is inadequate for mammary carcinoma, and may well be replaced by a minimum 9 year period.

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CARCINOMA OF THE COLON AND RECTUM

A Study of Metastasis and Recurrences

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SUCCESS in the management of cancer of the colon and rectum customarily is evaluated in terms of survival rates over arbitrarily determined periods. Unfortunately, from the standpoint of the accuracy of such estimations, factors other than the cancer per se may act to curtail survival. A patient who has had his cancer completely extirpated may succumb to a pulmonary embolus a week later. As far as this individual patient is concerned, the treatment has been a failure although from a purely technical standpoint it was highly successful. However, had the patient not fallen victim to an unfortunate postoperative complication, the most important thing in determining his survival would have been the success attending the efforts of the surgeon to eradicate the cancer.

The present study concerns itself entirely with the technical side of the problem, namely, the ability of the surgeon to rid the patient of cancer. The influence of metastatic growths, their distribution in the body, the accuracy with which their presence can be detected by the surgeon, and, finally, the question of recurrence will likewise be considered.

MATERIAL

During the 5 year period beginning January 1, 1935, and ending December 31, 1939, 334 patients suffering from carcinoma of the colon and rectum died and were subjected to postmortem examination. The material employed in this study was obtained from the clinical records and protocols of the necropsies of these patients. Only cases of primary adenocarcinoma were considered. (This excluded 1 squamous cell epithelioma of the rectum, 1 sarcoma of the cecum, 1 case of Hodgkin's disease of the cecum, and 3 cases of carcinoma secondary to lesions elsewhere in the digestive system.) The distribution of the lesions was as follows: rectum, 83 cases, or 24.9 per cent; rectosigmoid, 41 cases, or 12.3 per cent; sigmoid, 77 cases, or 23.1 per cent; descending colon, 18 cases, or 5.4 per cent; splenic flexure, 10 cases, or 3.0 per cent; transverse colon, 13 cases, or 3.9 per cent; hepatic flexure, 11 cases, or 3.3 per cent; ascending colon, 24 cases, or 7.2 per cent; cecum, 29 cases, or 8.7 per cent, and 28 cases of multiple carcinomas, or 8.4 per cent. This distribution corresponds in general to the clinical distribution encountered at the Mayo Clinic and elsewhere (Lockhart-Mummery). The incidence of multiple carcinomas is higher than that reported by Bargen and Rankin or Schweiger and Bargen, owing to the fact that we included 8 cases of multiple polyposis with multiple malignant lesions and 5 cases in which two or more low grade polypoid malignant lesions were present.

From the Division of Surgery, Mayo Clinic and Mayo Foundation.

FINDINGS

Metastasis. In order to determine the total incidence of metastatic growths and their distribution, the findings of the surgical pathologist at the time of operation (in those cases in which patients were subjected to surgical procedures), as well as those of the pathologist who made the postmortem examination, were consulted. Only those tissues showing microscopic as well as gross evidence of invasion were listed as sites of metastasis. It is to be remembered that these figures represent totals and are therefore higher than the surgical or postmortem figures alone. The findings appear in Table I.

The highest total incidence of metastasis occurred in cases of carcinoma of the transverse colon, followed by those of the rectosigmoid and splenic flexure, while the lowest incidence occurred in those of the hepatic flexure. When lesions of the transverse colon and multiple lesions are excluded, the incidence of metastasis is found to be 4.9 per cent higher from the left portion of the colon than from the right portion of the colon. The highest incidence of involvement of the regional lymph nodes occurred with carcinoma of the rectosigmoid, the second highest with carcinoma of the cecum, and the lowest with carcinoma of the splenic flexure. Carcinoma of the rectosigmoid likewise led in the incidence of hepatic metastasis. Metastasis to the lungs and pleura most commonly followed carcinoma of the rectum.

TABLE I.—INCIDENCE AND DISTRIBUTION OF METASTATIC GROWTHS

Site of primary tumor	Rectum	Recto-sigmoid	Sigmoid	Descending colon	Splenic flexure	Transverse colon	Hepatic flexure	Ascending colon	Cecum	Multiple tumors	Total
Cases	83	41	77	18	10	13	11	24	29	28	334
Per cent without metastasis	44.6	29.3	37.7	44.4	30.0	23.1	54.5	41.7	41.4	42.9	39.5
Per cent with metastasis	55.4	70.7	62.3	55.6	70.0	76.9	45.5	58.3	58.6	57.1	60.5
Per cent of total											
Regional nodes	42.2	58.5	44.1	38.9	30.0	53.8	36.4	50.0	55.2	53.6	47.0
Distant nodes	6.0	2.4	6.5	0	10.0	7.7	0	8.3	3.4	3.6	5.1
Liver	21.7	31.7	26.0	11.1	20.0	15.4	27.3	20.8	13.8	17.9	22.2
Lungs and pleura	16.9	7.3	7.8	5.6	0	0	9.1	12.5	10.3	10.7	10.2
Other	18.1	24.4	36.4	5.6	50.0	53.8	27.3	37.5	31.0	10.7	26.9
Per cent showing local invasion	28.9	43.9	44.2	50.0	70.0	61.5	36.4	33.3	48.3	17.9	39.2

Peritoneal implants were found in 11.7 per cent of the cases. Other sites of metastasis included the jejunum or ileum, 6.6 per cent; omentum, 4.5 per cent; adrenals, 3.9 per cent; ovaries, 3.6 per cent; stomach, 3.0 per cent; pancreas and bladder, 2.4 per cent each; colon, 2.1 per cent; spleen, prostate, ureters, and diaphragm, 1.8 per cent each; mesentery, abdominal wall, and kidneys, 1.5 per cent each; duodenum, gall bladder or bile passages, bony skeleton, 1.2 per cent each; mesenteric, portal or hepatic veins, fallopian tubes, 0.9 per cent each; wound, uterus, vagina, iliac veins or vena cava, 0.6 per cent each; skin or subcutaneous tissue, sympathetic ganglia, mesenteric artery, rectum, myocardium, and brain, 0.3 per cent each. In most of the cases in which visceral metastasis occurred, involvement of the lymph nodes was noted, but this was not a constant finding.

In addition to metastatic implants, the tendency to local invasion is indicated in Table I. Invasion was said to have occurred when there was histological evidence of serosal involvement or penetration to adjacent tissues by the carcinomatous process. This is seen to have taken place most commonly in cases of carcinoma of the splenic flexure and least commonly in cases of multiple tumors.

A more detailed investigation of metastatic growths in the liver was carried out to ascertain whether the site of the primary tumor had any influence on the location of the implants in the liver. It will be recalled that lesions of the left portion of the colon were more common than those of the right, and that the incidence of metastasis was slightly higher from the left portion of the colon than from the right. There were 74 cases in which metastatic growths occurred in the liver. In 5 cases—4 of which came from lesions of the rectum or sigmoid—these were confined to the left lobe; in 3 cases they were predominantly in the left lobe; in 48 cases there was diffuse involvement of both lobes; in 4 cases the right lobe was chiefly involved, and in 14 cases it was exclusively involved. In other words, involvement of the right lobe preponderated in 24.3 per cent of the cases, of the left lobe in 10.8 per cent.

Recognition of metastatic growths. In order to determine the degree of accuracy with which the surgeon was able to recognize the presence of

TABLE II.—EVIDENCE OF EXTENSION OF CARCINOMA IN GROUP OF CASES IN WHICH NO EXPLORATION WAS CARRIED OUT
(Postmortem findings)

Therapeutic class	Cases	Per cent of cases without metastasis	Per cent of cases with metastasis	Per cent of cases with regional nodes involved	Per cent of cases with hepatic metastasis	Per cent of cases with other metastasis	Per cent of cases with local invasion
No operation	22	18.2	81.8	72.7	50.0	54.5	50.0
Emergency operation	18	44.4	55.6	44.4	33.3	33.3	33.3
Fulguration or irradiation or both	9	44.4	55.6	33.3	44.4	44.4	22.2
Incidental postmortem finding	21	95.2	4.8	4.8	0	0	4.8
Total	70	51.4	48.6	40.0	30.0	31.4	28.6

TABLE III.—CASES IN WHICH ABDOMINAL EXPLORATION WAS CARRIED OUT

Operative procedure	Cases	Findings	Per cent of cases in which no metastasis was found	Per cent of cases in which metastasis was found	Per cent of cases with regional nodes involved	Per cent of cases with hepatic metastasis	Per cent of cases with other metastasis	Per cent of cases with local invasion
Exploration only	13	Operation	30.8	69.2	0	53.8	38.5	0
		Necropsy	15.4	84.6	69.2	69.2	61.5	46.2
Palliative operation	38	Operation	26.3	73.7	23.7	42.1	42.1	68.4
		Necropsy	5.3	94.7	60.5	57.9	68.4	71.1
Preliminary operation	44	Operation	81.8	18.2	2.3	(4.5?)	11.4	(38.6?)
		Necropsy	47.7	52.3	34.1	11.4	27.3	36.4
Total	95	Operation	52.6	47.4	10.5	26.3	27.4	45.3
		Necropsy	26.3	73.7	49.5	37.9	48.4	51.6

metastatic growths at the time of operation, an analysis of the cases was made on the bases of the procedures to which each patient was subjected. The cases were divided into two main groups. The first consisted of 70 cases in which no exploration was carried out. This included 22 cases, 6.6 per cent of the total, in which no operation was performed, 18 cases, 5.4 per cent, in which emergency operations were performed because of obstruction or perforation of the bowel and in which exploration was not feasible, 9 cases, 2.7 per cent, in which treatment was given by fulguration or irradiation or both, and 21 cases, 6.3 per cent, in which the tumors were incidental findings at postmortem examination. The second group consisted of 264 cases in which opportunity was afforded for exploration of the abdominal cavity by the surgeon. This group included 13 cases, 3.9 per cent, in which exploration alone was carried out, 38 cases, 11.4 per cent, in which palliative[1] procedures were carried out, 44 cases, 13.2 per cent, in which preliminary operations—such as colostomy or ileocolostomy in anticipation of subsequent resection—were performed, and finally, 169 cases, 50.6 per cent, in which presumably curative operations—resections—were performed.

Since the cases in the first group afforded no opportunity for the surgical recognition of metastatic growths, the postmortem findings alone were presented in Table II, chiefly for comparison with the findings in the second group. As would be expected, the highest incidence of cancerous extension, by local invasion or by metastasis, occurred in the group of cases in which no operation was performed because of the debility of the patient or clinical evidence of widespread metastasis. Likewise, the lowest percentage occurred in the group of small and unsuspected early carcinomas which were incidental postmortem findings.

In the group of cases in which the opportunity for exploration was afforded, a comparison of the operative and postmortem findings in the cases in which exploratory, palliative, or preliminary operations were performed is presented in Table III. The surgeon's opinion regarding local invasion and all metastatic growths except those in the liver was credited only when borne out by the findings of the surgical pathologist. In the case of metastatic growths in the liver the surgeon's opinion was recorded regardless of confirmation, which was seldom practicable. The average length of survival after operation was 43.7 days after exploration, 66.3 days after palliative procedures, and 16.8 days after preliminary operations. Marked discrepancies are seen to exist in the incidence of involvement of the lymph nodes between the operative and postmortem findings. These can be explained by the fact that in comparatively few of the cases in this group were the regional nodes removed for examination by the surgical pathologist. The ability of the surgeon to detect metastatic growths in the liver was fairly accurate, as will be shown later. The discrepancy in the case of other metastatic growths is due to the fact that only those which lay within the peritoneal cavity could be detected readily. Local invasion is seen to have occurred in 71.1 per cent of the cases in which palliative procedures were performed and in only 5.3 per cent of these cases were there no metastatic growths. The high incidence of metastasis—52.3 per cent—in cases in which patients were subjected to preliminary operation is of interest, as it indicates that many of these cases would not have been suitable for resection had the patients survived.

[1]Operations were designated as palliative not only when, because of local extension or the presence of metastasis, no attempt was made to remove the tumor and decompression or short circuiting alone was established, but also when resections were carried out in the presence of obvious metastatic growths in the liver or extensions of the tumor which could not be removed.

TABLE IV.—CASES IN WHICH CURATIVE RESECTIONS WERE PERFORMED

Survival after operation	Cases	Operative findings					Postmortem findings					
		Evidence of spread of tumor	Per cent of cases	Mode of spread in cases with extension			Per cent of cases in which no metastasis was found	Per cent of cases in which metastasis was found	Distribution of metastasis			Per cent of cases in which residual or recurrent carcinoma was found
				Invasion	Nodes	Other			Nodes	Liver	Other	
More than 21 days	38	No extension	31.6				58.3	41.7	25.0	16.7	25.0	16.7
		Extension	68.4	76.9	53.8	23.1	50.0	50.0	26.9	15.4	38.5	11.5
		Total	100.0				52.6	47.4	26.3	15.8	34.2	13.2
21 days or less	131	No extension	38.9				82.4	17.6	7.8	5.9	2.0	3.9
		Extension	61.1	60.0	68.8	10.0	65.0	35.0	11.3	10.0	13.8	6.3
		Total	100.0				71.8	28.2	9.9	8.4	9.2	5.3
Total	169	No extension	37.3				77.8	22.2	11.1	7.9	6.3	6.3
		Extension	62.7	64.2	65.1	13.2	61.3	38.7	15.1	11.3	19.8	7.5
		Total	100.0				67.5	32.5	13.6	10.1	14.8	7.1

In Table IV are seen the findings in those cases in which supposedly curative operations were performed. There were 169 such cases. These were divided into two groups, those in which death occurred within 3 weeks of operation—131 cases—and those in which survival exceeded 3 weeks—38 cases, in some of which the patients lived several years after operation. In the latter group of cases, the surgeon found no evidence of extension of the tumor beyond the confines of the bowel in 12, or 31.6 per cent, of the cases. In 7, or 58.3 per cent, of those in which no extension was found, no metastatic growths were found at necropsy. In the remaining 5, 41.7 per cent, metastatic growths were found at necropsy, involving the lymph nodes in 3, 25.0 per cent, the liver in 2, 16.7 per cent, and other regions in 3 cases, 25.0 per cent. Residual carcinoma was found in 2 cases, 16.7 per cent. In the 26 cases in which the surgeon found evidence of extension—local invasion in 20 cases, metastasis to nodes in 14, metastasis elsewhere in 6—no metastatic growths were found at postmortem examination in 13 cases, 50.0 per cent. Metastatic growths found in the 13 remaining cases were located in the lymph nodes in 7 cases, 26.9 per cent, the liver in 4, 15.4 per cent, and elsewhere in 10, 38.5 per cent. Recurrent or residual cancer was noted in 3 cases, 11.5 per cent.

The most interesting group of cases from the standpoint of the study at hand is the group in which resection was carried out and death occurred within 3 weeks of the time of operation, as the result of postoperative complications, such as shock, hemorrhage, pneumonia, peritonitis, or pulmonary embolism. The findings in those cases presumably should differ very little from the conditions left by the surgeon at the conclusion of the operation, at least in so far as the status of the tumor is concerned. In this group of 131 cases, the surgeon found no evidence of extension in 51 cases, 38.9 per cent. When these 51 cases came to necropsy, no metastatic growths were found in 42, or 82.4 per cent. Of the 9 remaining cases, 17.6 per cent, the pathologist found metastatic growths in lymph nodes in 4, or 7.8 per cent, in the liver in 3, or 5.9 per cent, and elsewhere in 1, or 2.0 per cent. Residual carcinoma was found in 2 cases, 3.9 per cent. In the 80 cases, 61.1 per cent, in which the surgeon found evidence of extension—local invasion in 48 cases, metastasis to lymph nodes in 55 cases, and other metastasis in 8 cases—52, or 65.0 per cent, were free of metastatic growths at postmortem examination. In the 28 remaining cases, 35.0 per cent, metastatic growths were found in lymph nodes in 9 cases, 11.3 per cent, in the liver in 8 cases, 10.0 per cent, and elsewhere in 11, or 13.8 per cent. Residual carcinoma was detected in 5 cases, 6.3 per cent. Considering all cases in which resection was carried out, the surgeon found no extension in 37.3 per cent; of these, 77.8 per cent were free of metastatic growths at necropsy. He found extension in 62.7 per cent and 61.3 per cent of these were free of metastatic growths at necropsy. Residual carcinoma was found in 7.1 per cent.

The responsibility of recognizing metastatic growths does not fall on the surgeon alone. Pulmonary, skeletal, certain hepatic metastatic growths, and many others often can be discovered by the clinician or roentgenologist and the patient

may be spared futile and unnecessary operations. On the surgical pathologist rests the duty of identifying involved lymph nodes and of confirming gross evidence of visceral metastasis. Next to the regional nodes, the liver is the site in which metastatic growths are found most frequently. Since biopsy of suspicious tissue in this organ is not practicable routinely, the discovery and recognition of carcinomatous implants fall to the surgeon. With what degree of aptitude the surgeon meets this responsibility, the following study indicates.

In the entire series of 334 cases, there were 260 in which adequate opportunity for exploration of the liver by the surgeon was afforded. In 224 of these he considered the liver to be free of metastatic growths; in 12 there were areas which he regarded with suspicion, and in 24 cases, he felt that metastatic growths definitely were present. Of those cases in which the surgeon thought the liver was not involved, postmortem examination revealed an uninvolved liver in 197 cases, or 87.9 per cent, and a carcinomatous liver in 27, or 12.1 per cent. In the cases in which the surgeon was in doubt, the pathologist found metastatic growths in 6, or 50.0 per cent and none in 6, or 50.0 per cent. In those cases in which the surgeon believed metastatic growths to be present, the pathologist confirmed the impression in 22, or 91.7 per cent, but did not confirm it in 2 cases, or 8.3 per cent.

Factors contributing to recurrence. The most common cause of so called recurrence, in the broad sense of the term, probably is the failure to remove some portion of the primary growth or some of its secondary colonies. It is questionable, but possible, that in some cases implants may occur by contamination during the process of extirpation. But a very common cause, which usually does not receive the attention it merits, is the presence in the remaining segments of the bowel of areas bearing malignant or potentially malignant growths which have been wholly unsuspected. In the group of 169 cases in which curative resection was carried out, independent cancers were found in the bowel at necropsy in 7 cases, or 4.1 per cent.

Although unanimous agreement is not yet forthcoming as to the relation of adenomatous polyps to carcinoma of the large bowel, there is little room for doubt that in many cases the rôle played by polyps is more than coincidental. This impression certainly was borne out by the present study. Adenomatous polyps were found in 114, or 34.1 per cent, of the 334 cases reviewed. In these 114 cases, definite malignant changes were recognized in the polyps of 16, or 14.0 per cent. The adenomatous polyps occurred singly in 54 cases; multiple polyps were noted in 52 cases; diffuse polyposis coli existed in 8 cases. In 15 cases the polyps were confined to the rectum; in 20, to the sigmoid; in 8, to the descending colon; in 10, to the transverse colon; in 7, to the ascending colon, and in 10, to the cecum. In 39 cases they were distributed over several segments. In 5 cases their location was not noted.

For purposes of comparison a review was carried out of 100 consecutive postmortem examinations performed on adults who had died of diseases other than carcinoma of the large bowel. Their ages ranged from 22 to 80 years, with an average age of 54.7 years. Polyps were present in 16 cases, 16.0 per cent. Eight of these, 50.0 per cent, showed beginning cancerous changes.

The true importance of adenomatous polyps appears when one considers the group of cases in which death occurred within 3 weeks of resection. Any polyps found in this group of 131 cases in all probability were present at the time of operation. They were found at postmortem examination in 49 of these cases, or 37.4 per cent. In 7, or 14.3 per cent, malignant changes had occurred.

OBSERVATIONS

Extension of carcinoma of the colon and rectum may take place by local invasion, via the lymphatics or via the blood stream. Extension is the chief factor influencing operability. Local infiltration is the most common form and spread by the other routes is said to occur relatively late. The extent of spread by the respective routes varies with different portions of the colon. We found local invasion most common with lesions of the splenic flexure, a fact which probably accounts for the high mortality rate attending removal of growths in this region. Invasion occurred with 28.9 per cent of the rectal carcinomas. Bargen and Larson noted it in 109 of 447 cases of rectal carcinoma. Attachments most commonly result from inflammation but, in our series, only cases in which actual invasion of the tumor was demonstrated were included.

We found regional nodes involved in 47 per cent of our cases. There was no progressive segmental increase or decrease extending from one end of the colon to the other. Boyd stated that spread is slowest in the distal portion of the colon and danger of recurrence is greatest in the proximal portion because of the more abundant lymphatics associated with the absorptive function of the latter. Rankin (21), on the other hand, found metastatic growths most common in the distal portion of the colon, least common in the proximal

portion, and attributed this distribution to the protective influence exerted by the lymphatics. We found involvement of the regional lymph nodes most common with carcinoma of the rectosigmoid—58.5 per cent—but almost as common with cecal lesions—55.2 per cent. Craig and MacCarty found the lymph nodes involved with 32 per cent of the carcinomas of the cecum, while McVay found involvement with 47 per cent of rectal carcinomas. These figures were based on operative specimens and, accordingly, are lower than ours. However, Gilchrist and David found 68 per cent nodal involvement in their painstaking study of specimens of carcinoma of the rectum removed at operation.

Examination of the regional lymph nodes at the time of operation is of great importance in establishing a prognosis. Many attempts have been made to discover factors influencing nodal involvement. Naturally, the longer a growth has been present, the greater the likelihood of extension. Rankin and Broders found that the incidence of nodal involvement paralleled the grade of the tumor—based on histological evidence of differentiation. Bacon and Gilbert stated that invading types of lesions are most likely to metastasize and Hayes, in his study of 100 cases of colonic cancer, found metastasis least common with growths which protruded into the lumen of the bowel.

Visceral metastatic growths were most common in the liver, the lungs and pleura coming second. Such metastatic growths occurred most often from carcinoma of the rectum or rectosigmoid in our series. This was in accord with the observations of Harding and Hankins, who also noted the tendency of rectal lesions to produce visceral metastasis. Involvement of such structures as the bladder, other segments of the alimentary canal, and the abdominal wall was usually by direct extension rather than true metastasis. Ovarian involvement was sometimes by direct extension, sometimes blood-borne, giving rise to a Krukenberg tumor. Visceral metastatic growths may be chiefly lymph-borne or blood-borne. It generally is stated that evidence of nodal involvement is the most reliable indication of the presence of visceral metastatic growths. Rankin and Broders found the incidence of visceral metastasis paralleling the grade of the primary lesion. Brown and Warren, however, expressed the belief that the most valuable index of all is evidence of vascular invasion, as determined by careful study of 3 regions of the primary tumor. They noted visceral metastasis with 41 per cent of 170 cases of rectal carcinoma. In many of these cases no evidence of nodal involvement was found but in only 1 case did visceral metastasis occur in the absence of local intravascular invasion.

Our study of the distribution of metastatic growths in the liver was not particularly fruitful. Injection experiments by McIndoe and Counseller and others have suggested that the right and left lobes of the liver are anatomically independent in regard to their blood supply and excretory ducts. Such work has given rise to the question of the existence of a dual portal current, blood from the superior mesenteric vein (jejunum, ileum, and right portion of the colon) passing mainly to the right lobe, and blood from the lienal vein (stomach, left portion of the colon, rectum, and spleen) passing to the left. Although metastatic growths were most commonly diffuse, regardless of the site of the primary lesion, when there was a preponderance, it occurred more than twice as often in the right lobe as in the left, although lesions of the left portion of the colon and rectum were far more common than those of the right portion of the colon. This discrepancy could not be accounted for by a difference in the relative weights of the two lobes, which it is said rarely exceeds 100 grams.

In considering the problem of ridding the patient of his disease, only the group of 169 cases in which resection was carried out need be reviewed. In only 37.3 per cent of these cases was there no evidence of extension at the time of operation. Lymph nodes were involved in 40.8 per cent, involvement of overlying peritoneum or adjacent tissues had occurred in 40.2 per cent, and other metastatic growths were found in 8.2 per cent: 65.1 per cent, 64.2 per cent, and 13.2 per cent, respectively, of the cases which showed extension. In spite of this comparatively high incidence of extension, no metastatic growths were found at postmortem examination in 67.5 per cent and recurrent or residual carcinoma in only 7.1 per cent. In the group of 131 cases in which survival was 3 weeks or less and in which conditions presumably differed little from those at the completion of operation, it is found that, when no extension was noted at operation, metastatic growths could be discovered in only 17.6 per cent at postmortem examination and residual carcinoma in only 3.9 per cent. Furthermore, of the cases in which extension was noted at operation, only 35 per cent showed metastatic growths at necropsy, and 6.3 per cent residual cancer. Obviously, minute undiscovered metastatic growths may have remained, but the fact that gross evidence of cancer remaining anywhere in the body was absent in so high a proportion of cases after opera-

tion, even though extension was known to have occurred, reflects considerable credit on the efforts of the surgeon. In the group in which survival exceeded 3 weeks, sometimes by several years, an increase of 19.2 per cent in the incidence of metastatic growths was found at necropsy, distant metastatic growths which were beyond the scope of surgical intervention showing the greatest relative increase. Residual cancer increased 7.9 per cent but recurrences or new cancers probably contributed to this rise.

The foregoing figures and those of the other groups in which procedures other than resection were carried out, likewise furnish a fairly good index of the accuracy with which metastatic growths could be detected at operation. The recognition of metastatic growths is the determining factor in deciding whether an operation is to be an exploration alone or a palliative one, or whether resection is to be attempted, and if the latter, how much tissue can and must be removed. The surgeon overlooked metastatic growths in the liver in only 12.1 per cent of cases. Many of these growths were small and were discovered a long interval after surgical exploration. When suspicious areas were noted at operation, necropsy showed 50 per cent of them to be malignant, and finally, when the surgeon designated the liver as involved, he was correct 91.7 per cent of the time. Lesions in the liver which were potential sources of confusion to the surgeon were revealed at necropsy to include adenomas of the bile ducts, cysts, hemangiomas, tubercles, infarcts, and cirrhosis.

The importance of the presence of additional, independent lesions of the bowel in the development of recurrences has been shown by the findings at necropsy of additional cancers in 7 cases and cancerous polyps in 10 cases in the group in which resection was performed. The rôle of adenomatous polyps may be controversial but their presence in 34.1 per cent of all the cases of carcinoma of the colon and rectum in this study, in contrast to 16.0 per cent incidence in a group of patients of similar age who died from other causes, is suggestive, to say the least. Adenomatous polyps were left after operation in 34.3 per cent of the group in which resection was performed, the incidence of malignant polyps and frank secondary carcinomas being slightly higher in the group of cases in which the survivals were longer. The 50 per cent incidence of malignant changes in the polyps of the control group may seem incongruous at first sight until one recalls that the polyps in the series under consideration were associated with carcinomas in 100 per cent and, when one speaks of malignant changes in 17.2 per cent of the cases in which polyps were present, one is speaking of polyps still left behind after resection of a full blown cancer.

Just as senile hyperplastic changes develop in the epidermis with advancing age, hyperplastic tendencies develop in the intestinal mucosa. Bargen stated that some form of polypoid hyperplasia of the mucosa is present in 50 per cent of persons more than 30 years of age. The frequency with which polyps occur is difficult to estimate. Clinically, Buie has found them in 1 of every 35 patients undergoing proctoscopic examinations; polypoid lesions are seen in 1.8 per cent of the colons examined roentgenologically at the Mayo Clinic. Pathologically, Stewart has shown that the reported incidence of polyps varies with the care with which they are sought. He found them associated with 29.6 per cent of the cancers of the colon that he studied. Susman found polyps in 6 per cent of 1,100 consecutive postmortem examinations. Only 7 per cent of these polyps occurred in persons less than 40 years of age, although 40 per cent of his cases fell into this age group. Fifteen of his 66 patients having polyps had cancer of the colon and, among 34 cases of cancer of the colon, polyps were present in 15, the peak of incidence of both lesions falling between the ages of 50 and 70 years.

The most suggestive evidence of the relation of adenomatous polyps to cancer is found in the familial cases, although these tend to occur in younger age groups. Rankin (21) stated that cancer of the colon develops in 50 per cent of these cases. FitzGibbon and Rankin, David, and others, by careful pathological studies, have traced the development of cancer from polyps. In examination of patients who had refused to submit to fulguration, Buie has seen carcinoma at the site previously occupied by polyps. Lockhart-Mummery and Dukes described mucosal irregularity adjacent to cancers of the colon, localized areas of epithelial hyperplasia extending several inches away from the growth. They expressed the belief that adenomas represent a more advanced stage of this hyperplasia, which may develop into carcinoma in certain cases. The opinion was also expressed that after carcinoma has developed, hyperplasia and benign tumors regress.

The importance of the submucosal lymphoid aggregations in the production of these epithelial changes has been emphasized by Coffey and Bargen. More recently, an interesting investigation and review of the topic have been reported by Bargen, Cromar, and Dixon.

The origin of polyps sometimes is inflammatory, in association with such conditions as chronic ulcerative colitis, tuberculous enteritis, old strictures of the bowel, and so forth. Although these often are not true adenomatous polyps, occasionally they are. In 6 of our cases carcinoma of the large bowel developed in association with chronic ulcerative colitis. The question has even been raised whether the polyps occurring in connection with carcinoma of the bowel may not be the result of the irritating influence exerted by the presence of an ulcerating cancer. But hyperplastic and polypoid changes are more common around small, early carcinomas than around large, late lesions, according to Lockhart-Mummery and Dukes. Yeomans has emphasized the primary importance of irritation and inflammation in the development of polyps and carcinoma in accord with the old views of Virchow and of Verse.

Whether one believes that all cancers of the colon arise from polyps and that all polyps are potentially malignant, or not, there is no denying that accessory growths often are responsible for so called recurrences. The practical importance of this is apparent. Whenever a carcinoma of the colon is encountered, the presence of another malignant or potentially malignant lesion should be suspected and carefully ruled out. Having discovered a carcinoma by proctoscopic examination, the clinician should not settle back in the happy assurance of having fulfilled his obligation to the patient. In the absence of obstruction, roentgenologic study of the remainder of the colon should be carried out to eliminate the possible presence of another lesion. The entire colon should be explored carefully by the surgeon at the time of operation. All malignant lesions should be removed. Benign lesions should be removed, fulgurated, or kept under faithful observation. In all cases in which resection is performed, follow-up studies should be carried out at periodic intervals. There is considerable clinical and experimental evidence to support the hypothesis that the presence of a cancer inhibits the development of a second cancer. When the primary lesion is removed, this "restraining influence" disappears and another potentially malignant region may undergo carcinomatous degeneration.

It is beyond the scope of this paper to discuss the influences at work in the production of hyperplastic or malignant changes or changes which normally hold cell growth and regenerative processes in check. Yet the subject is not so controversial but that certain of its connotations should be borne in mind by all who are called on to diagnose and treat carcinoma of the colon and rectum. Only by thorough and painstaking investigations of each case will avoidable "recurrences," due to accessory lesions, be prevented.

SUMMARY

A clinicopathological study of 334 cases of carcinoma of the colon and rectum has been presented. Regional or distant metastasis occurred in 60.5 per cent of the cases and local invasion in 39.2 per cent. Among cases in which there was hepatic metastasis, no correlation could be found between the site of the primary tumor and the site of involvement in the liver.

The ability of the surgeon to detect metastasis at the time of operation was found to be good. Among cases in which death occurred shortly after resection, no metastasis was found at necropsy in 82.4 per cent of those in which none was found at operation. The success of extirpation was revealed in this same group of cases, 65 per cent of those in which there was metastasis at operation being free of it at necropsy. Residual cancer was found in only 5.3 per cent of the cases in which death occurred shortly after resection. In those cases in which the surgeon believed metastatic growth to be present in the liver, the pathologist confirmed the impression in 91.7 per cent.

Independent growths are felt to be responsible for many "recurrences." Polyps were present in 34.1 per cent of the cases in this entire series, in contrast to 16.0 per cent of a control series consisting of patients without cancer of the bowel. In 14.0 per cent of the cases in which polyps occurred, malignant changes were found in the polyps. Multiple carcinomas were found in 8.4 per cent of the cases. Among cases in which resection was carried out, additional independent cancers were found at necropsy in 4.1 per cent.

Whenever a carcinoma is found in any portion of the colon or rectum, the presence of a second carcinoma must be carefully ruled out. After operation, the malignant potentialities of the remaining mucous membrane should be borne in mind and careful follow-up studies carried out.

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AN ARTIFICIAL ILEOCECAL VALVE

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IT has been established that the normal ileocecal valve serves two important physiological functions; namely, (1) to avoid too rapid emptying of ileal contents into the cecum, thereby permitting maximal digestion and absorption of food products, and (2) to prevent a reflux of fluids, laden with great numbers of bacteria and with toxic end products from putrefaction, into the rapidly absorbing ileum. Besides this protective mechanism furnished by the valve, there is, of course, the relatively great abundance of lymphoid tissue, in the form of "Peyer's patches," in the walls of the terminal segments of the ileum. These, as Huntington concluded from his investigations, protect the body from invasion by microorganisms in that stretch of the gastrointestinal tube. It is particularly in the cecum, where the presence of a liquid nutrient medium represented by the fluid intestinal content or feces is conducive to luxuriant bacterial growth that the danger of bacterial invasion is great. That the strain on the protective mechanism of the junction of small and large intestine is considerable is indicated by the frequency with which that lymphoid tissue breaks down with resultant peritonitis and often death.

According to Alvarez and Rankin, the mucosa of the colon, on the other hand, appears to be a very efficient barrier to the passage of toxins into circulation. One of the features that is said to protect the body from autointoxication is the dryness of the feces in the middle and descending portions of the colon. About the only place in which absorption of bacteria and their toxins and the end products of protein putrefaction are likely to occur is in the first part of the colon, where the fecal material is sufficiently liquid, although toxins that are absorbed here are believed to be slightly altered by the mucosa of the colon and by the liver. Rankin states that "more dangerous and more deleterious to health than the passage of chemical substances is probably the passage of bacteria from the cecum and terminal portion of the ileum into the lymph passages and nodes of the mesentery."

A number of investigators have shown that bacteria are constantly getting through the wall of the bowel, and there is evidence that at times, as may occur after purgation or after intestinal upsets, this grade of infection of the lymph nodes or of the blood stream is severe enough to injure health. Excepting perhaps the mouth and the pharynx, the ileocecal area of the gastrointestinal tract, for the reasons stated, is most vulnerable and most exposed to attack by bacteria and their toxins.

On the basis of the incompetence of the ileocecal valve seen by x-ray examination in some patients with gastrointestinal complaints, the opinions expressed by many roentgenologists differ greatly regarding its significance. Hurst declares unequivocally that the ileocecal sphincter does not prevent regurgitation into the ileum. He has seen bismuth suspension pass into the ileum when run into the colon at a pressure as low as 1 foot of water. "There can be no doubt," he says, "that the function of the sphincter is, as Keith suggested, to prevent the contents of the ileum from passing too rapidly into the cecum." Barclay and others are of the opinion that the competence or the incompetence of the ileocolic valve is of no significance in diagnosis. Singer and Holtzknecht observed incompetence in numerous cases of obstipation, and this occurred whether the cecum was filled or not. Carmen declares that incompetence of the ileocecal valve is of all degrees, ranging from a trivial backflow to an extensive filling of the lower ileum.

Of those who regard incompetency of the ileocecal valve as a significant factor in diagnosis are Case, Dietlen, Ivy, Carmen, and others. Dietlen states that while the ileocecal valve is incompetent in infants, it is normally competent in children and adults. Case has observed a reflux of ingested bismuth suspension from the colon to the ileum in many cases and believes that valvular incompetency is a significant abnormality, and that it is a common cause of ileal stasis. Carmen doubts that an enema, put into the bowel under unphysiological conditions which necessitate at least a slight degree of hydrostatic pressure, would be a fair test of the physiological competence of the valve. A regurgitation of ingested material into the ileum after once passing the ileocolic valve would, he claims, theoretically have much greater import. Whether incompetency of the ileocecal valve indicates an unimportant perversion or a laxity of function or is significant of

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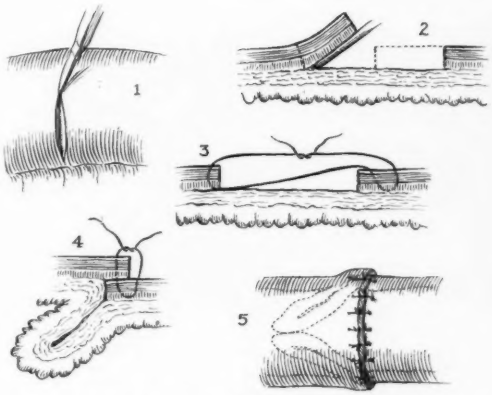


Fig. 1. *1*, Surface view, showing circumferential incision passing through the serous and muscular coats. *2*, Longitudinal section, showing the manner of elevating the flaps by blunt dissection, and the removal of the flaps to denude the intestinal segment. It should be noted that the instrument should pass through the submucosa as the line of cleavage. *3*, Passing of the stitch from the left edge of the denuded stretch over and through the right edge. *4*, *5*, Drawing together of the sutures, with approximation and overlapping of the edges, and the invagination of the circular mucosal fold.

serious pathology, with possibilities in the way of differential diagnosis, remains to be determined. Some surgeons, notably Kellogg, considered ileocecal incompetence of sufficient significance to devise methods for its repair.

Physiological studies of the functions of the ileocecal valve have been carried out by such investigators as Ivy, Wright, Starling, Hartridge and Evans, and others. Their conclusions are quite in accord with one another; namely, that the function of the ileocolic sphincter is to retain chyme in the ileum until digestion and absorption are completed and to prevent regurgitation of fecal material into the ileum.

With the belief that the surgeon does not give sufficient consideration to the physiological significance of an ileocecal valve when he chooses to do reconstructive surgery of the bowel, such as ileocolostomy and ileosigmoidostomy, I turned to the development of a technique for the utilization of a segment of the intestine in the formation of a valve resembling the ileocecal valve grossly, histologically, and physiologically.

In surgical procedures in which there is need of doing "short-circuiting" operations, such as ileocolostomy and ileosigmoidostomy, the operator, after severing the distal portion of the ileum and anastomosing the proximal end to the transverse or the sigmoid colon, invariably fails to reconstruct the normal anatomy, that is, he makes no attempt to reproduce a valve-like structure somewhere in the anastomosis.

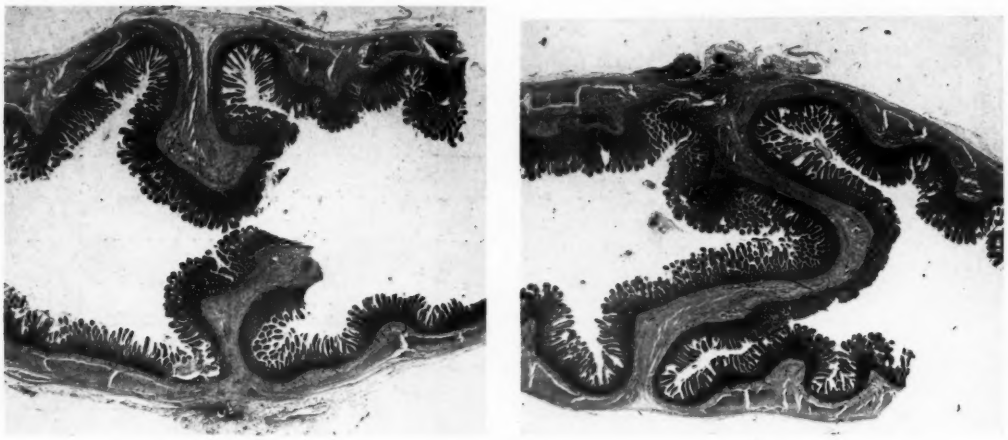
Fig. 2. Photograph of a longitudinal section of the gross specimen of the ileum containing the newly formed valve. Slightly magnified.

In the experiments of reproducing intestinal valves that should resemble the true ileocecal valve, dogs were used. In addition to developing a technique for the formation of such a valve, I made a preliminary comparative study of the bacterial flora in the small intestine of the animals in which ileocolostomies were made with and without the incorporation of the newly constructed valve.

OPERATIVE PROCEDURE

The method described in the following furnishes an ileocolic valve of excellent function, and the experimental cases in which it was introduced and subjected to trial have proved its competency throughout the period of observation. In the process of its reconstruction, the valve can be made to project in a given direction, thereby permitting the passage of food substances to take place in that direction only and preventing a reflux in the opposite direction. Before the anastomosis of the small and the large bowel is undertaken, the valve-like structure is first formed in the distal segment of the ileum approximately 15 to 20 centimeters from the chosen site of ileocolostomy. By constructing the valve first, that is, before opening the bowel, the operator works in a strictly aseptic field.

Figure 1, *1*, illustrates a piece of small intestine in which a circumferential seromuscular incision is carefully made down to and through the submucosa almost up to the exterior surface of the mucosa. With the blunt end of the scalpel, as shown in Figure 1, *2*, the severed seromuscular layer is raised by dissection from both sides of the



a b

Fig. 3. Photomicrographs of stained longitudinal section through the segment of ileum containing the newly formed valve. ×50. a, Section passed through the center or apex of the valve; the absence of the mucosa from one part of its margin is an artefact. b, Section passed more tangentially through the valve. In both cases the muscular layer is seen to extend part way into the mucosal submucosal fold representing the valve.

incision. In the dog, each raised flap needs to be about 1.5 centimeters in extent; yet, in every case the extent of the flap depended upon the diameter of the small bowel selected. The flaps are then cut off at their base, as indicated in *2*, Figure 1, so that a section of bowel about 3 centimeters in length is now denuded or lacking its seromuscular coat. Knowing the direction in which the protrusion of the valve must point, that is, toward the lumen of the large bowel, the operator proceeds to invaginate the denuded mucosa into the lumen. To achieve the correct pointing of the valvular fold, say toward the left, as portrayed in Figure 1, *4* and *5*, the interrupted suture employed is placed through the left seromuscular edge (Fig. 1, *3*). Then the suture is continued through the right seromuscular layer, but approximately 7 to 10 millimeters from its free edge (Fig. 1, *3*). The suture is now drawn together and tied (Fig. 1, *4* and *5*), while an assistant helps to keep the mucosa invaginated. Several interrupted sutures of black silk, or of chromic catgut (No. 000) are successively placed until the edges of the entire intestinal circumference (Fig. 1, *5*) are brought together in such a way that the left edge overlaps the right. This brings about a maximum amount of invagination of the circular mucosal fold, which now serves as the valve (Fig. 2) by permitting the intestinal contents to pass toward the colon but preventing their reflux by virtue of its ability to constrict and approximate itself to the point of complete closure.

Because of the frequent postoperative distention (Jones) of the ileum near the point of anastomosis, the chosen site of the valve is safely beyond and should therefore not become incompetent as a result of that distention. Moreover, the ample distance between the anastomosis and the position of the valve provides for a better blood supply on both its proximal and its distal sides. From the photographs (Figs. 2 and 3, a and b) of longitudinal sections of the bowel containing the newly constructed valve, it is seen that the latter is a projecting fold with a central core of muscle and submucosa covered on both sides by mucosa.

The mechanical effectiveness and strength of such newly constructed valves were tested in some of the experimental dogs after sufficient time had elapsed to permit healing of the intestinal wounds. Clamps were placed on the bowel some distance (15 cm.) from the valve, both proximal and distal to it. Then water was injected under pressure into the distal segment until this became distended. A considerable distention and back pressure was necessary before the valve became incompetent and allowed the water to rush into the collapsed proximal segment of the bowel.

In addition to such experiments, fluoroscopic studies were made on exteriorized bowel segments containing the anastomosis. By means of a Luer syringe, a barium sulfate solution was injected into the colon and observed as it passed into the

loop of anastomosed ileum containing the artificial ileocecal valve. The distal loop of the ileum became markedly distended before the barium was actually seen streaking into the loop of the ileum proximal to the valve. Apparently, the continued distention and the increasing back pressure of the barium rendered the valve incompetent.

Films were taken to illustrate further the efficiency and mechanism by which the return flow of colonic content is prevented from passing beyond the selected site of the artificial ileocecal valve.

In Figure 4, a, an exteriorized segment of colon from an experimental animal was clamped off on both sides of the ileocolic anastomosis and filled with barium sulfate solution. The site of the ileocolic union is seen to be distended, which indicates that the actual point of anastomosis offers no barrier to the reflux of the colonic material into the ileum. On the other hand, the site and actual outline of the artificial ileocecal valve is clearly made out in Figure 4, b. The shadow cast by the barium is bifurcated at the site of the valve, and this contour of shadow results from the fact that the valve is teat-like or cone-like with its apex pointing toward the ileocolic junction. As the barium backed into the space between the protrusion of the valve and the surrounding wall of the bowel, its pressure probably contributed to the closure of that orifice. In the same figure some barium is seen streaking through the valvular aperture.

Fig. 4. a, An exteriorized segment of colon clamped off on both sides of the ileocolic anastomosis and filled with barium. The actual site of anastomosis offers no barrier to the reflux of the colonic material into the ileum. b, A shadow cast by barium that is bifurcated at the site of the valve; this shadow represents the true contour and direction of the teat-like valve.

BACTERIOLOGICAL STUDY

In consideration of the effect of such a valve on the bacterial flora in the intestinal canal proximal to it, a preliminary bacteriological study was undertaken on a group of dogs subjected to ordinary ileocolostomy and on another group subjected to valvular ileocolostomy of the kind just described. Though the number of animals used thus far is too small to permit final conclusions, the results obtained appear to be significant and sufficiently encouraging to urge a continuance of the investigation.

On culture of the material obtained from the dog's ileum, both on Endo's and plain media, Bacillus coli was found to be the predominant organism. In several instances Streptococcus fecalis was also isolated, but in association with Bacillus coli and in numbers far less than the latter. Therefore, the only method available for a comparative study of the bacterial flora in the two groups of animals was a quantitative determination; that is, a count of the number of pure colonies of Bacillus coli isolated.

To obtain the bacteria, 5 cubic centimeters of warm sterile water in a Luer syringe, fitted with a Wassermann needle, was injected into the lumen of the ileum and withdrawn again into the syringe. Samples were taken from 6 consecutive levels, at 30 centimeter (1 foot) intervals, orad of the valve. The samples thus obtained were collected separately in sterile test tubes and cultured the same day.

Six such sample specimens were cultured on both Endo's and plain media, and after 24 hours of incubation the quantitative estimations were made directly from the culture dishes as follows: 1+ was taken to express a growth consisting of from 1 to 25 colonies of Bacillus coli; 2+ from 25 to 50 colonies; 3+ from 50 to 100 colonies, or twice the number of the preceding; while 4+ expresses a growth so "heavy" that an accurate count could not be made.

To study the effect of the introduction of the operative procedure, whether it be an ordinary

TABLE I.—THE EFFECT OF ORDINARY ILEOCOLOSTOMY ON THE BACTERIAL FLORA IN THE ILEUM OF THE DOG

Dog No.	Operative steps	Days post-operative	Culture medium	Bacterial growth from the samples of intestinal material taken at the indicated distances orad of the ileocolic valve						
				Organism	30 cm. or 1 ft.	60 cm. or 2 ft.	90 cm. or 3 ft.	120 cm. or 4 ft.	150 cm. or 5 ft.	180 cm. or 6 ft.
1	First step		Endo's Plain	B. coli Strep. fecalis	2+	3+	2+	2+	2+	2+
	Second step	13 days	Endo's Plain	B. coli B. coli	4+	4+	3+	3+	3+	3+
2	First step		Endo's Plain	B. coli B. coli	3+	1+	3+	3+	3+	2+
	Second step	9 days	Endo's Plain	B. coli Strep. fecalis	4+	4+	4+	3+	4+ 2+	4+ 2+
3	First step		Endo's Plain	B. coli Strep. fecalis	4+	4+	4+	2+	No growth	
	Second step	14 days	Endo's Plain	B. coli B. coli	4+	4+	4+	3+	2+ Strep. 2+	No growth
4	First step		Endo's Plain	B. coli Strep. fecalis	2+ 1+	2+	2+	Strep. 1+	Strep. 1+	No growth
	Second step	14 days	Endo's Plain	B coli Strep. fecalis	3+ 1+	2+ 1+	2+ 1+	1+	1+	No growth
5	First step		Endo's Plain	B. coli B. coli	3+	3+	2+	2+	2+	No growth
	Second step	14 days	Endo's Plain	B. coli B. coli	3+	3+	3+	2+	2+	1+
6	First step		Endo's Plain	B. coli Strep. fecalis	4+	4+	4+	4+	4+	4+
	Second step	43 days	Endo's Plain	B. coli	4+	1+	3+	4+	One colony	One colony
7	First step		Endo's Plain	B. coli	No growth	No growth	No growth	No growth	No growth	No growth
	Second step	18 days	Endo's Plain	B. coli	No growth	No growth	1+ Strep. fecalis	Strep. fecalis	Strep. fecalis	Strep. fecalis

First or preoperative step: Obtaining the bacteria as described in the text.
Operation: Ileocolostomy.
Second or postoperative step: Reopening the animal some time later for the withdrawal of bacteria as described.

ileocolostomy or a valvular ileocolostomy, each dog was examined bacteriologically by the method indicated both before and a certain period after the operation. In this way comparative data were obtained for each individual dog, as set forth in Tables I and II. To interpret the results properly, the data as a group must be compared, but the preoperative and postoperative states of each dog should be considered as the significant points, since any dog normally may differ from the next in his bacterial flora, especially quantitatively. The incorporation of the results from the different animals in the same table is simply a matter of convenience.

By referring to Table I, dog 1, it is seen that 13 days after an ordinary ileocolostomy was performed, the bacterial count rose to more than twice the number of Bacillus coli present prior to the surgical operation. Similarly, dog 2 also shows a marked increase in its bacterial count 9 days following surgery. At 150 centimeters (5 ft.) it reveals Streptococcus fecalis in a considerable number, which apparently did not exist there before the anastomosis was made. In dog 3, no particular changes are noticed until the 120 centimeter (4 ft.) level in the ileum is reached. Here, after 14 days, the bacterial count rises from 2+ to 3+, thus indicating an increase of approximately two times the number of bacteria originally present. At a point 150 centimeters (5 ft.) it reveals Streptococcus fecalis in a considerable number, which apparently did not exist there before the anastomosis was made. In dog 3, no particular changes are noticed until the 120 centimeter (4 ft.) level in the ileum is reached. Here, after 14 days, the bacterial count rises from 2+ to 3+, indicating an increase of approximately two times the number of bacteria originally present. At a point 150 centimeters (5 ft.) in the ileal segment of the same animal, Bacillus coli and Streptococcus fecalis ap-

TABLE II.—THE EFFECT OF VALVULAR ILEOCOLOSTOMY ON THE BACTERIAL FLORA IN THE ILEUM OF THE DOG

Dog No.	Operative steps	Days post-operative	Culture medium	Bacterial growth from the samples of intestinal material taken at the indicated distances orad of the ileocolic valve						
				Organism	30 cm. or 1 ft.	60 cm. or 2 ft.	90 cm. or 3 ft.	120 cm. or 4 ft.	150 cm. or 5 ft.	180 cm. or 6 ft.
1	First step		Endo's Plain	B. coli B. coli	3+	1+	3+	3+	3+	No growth
	Second step	14	Endo's Plain	B. coli B. coli	3+	3+	3+	3+	3+	No growth
2	First step		Endo's Plain	B. coli Strep. fecalis	3+ 3+	3+	3+	3+	3+	3+
	Second step	14	Endo's Plain	B. coli B. coli	3+	3+	2+	2+	1+	No growth
3	First step		Endo's Plain	B. coli Strep. fecalis	4+ 3+	4+	3+	1+	2+	No growth
	Second step	14	Endo's Plain	B. coli B. coli	3+	3+	2+	2+	2+	No growth
4	First step		Endo's Plain	B. coli B. coli	2+	2+	No growth			
	Second step	9	Endo's Plain	B. coli B. coli	1+	1+	No growth			
5	First step		Endo's Plain	B. coli B. coli	4+	4+	3+	3+	2+	2+
	Second step	14	Endo's Plain	B. coli B. coli	4+	3+	3+	2+	2+	No growth
6	First step		Endo's Plain	B. coli B. coli	3+	3+	3+	1+	No growth	
	Second step	5 mo.	Endo's Plain	B. coli Strep. fecalis	2+ 1+	1+	No growth		1+	No growth
7	First step		Endo's Plain	B. coli	4+	4+	No growth			
	Second step	27	Endo's Plain	B. coli	3+	2+	1+	No growth		
8	First step		Endo's Plain	B. coli	4+	4+	4+	4+	4+	4+
	Second step	60	Endo's Plain	B. coli	4+	3+	2+	No growth		

First or preoperative step: Obtaining the bacteria as described in text.
Operation: Valvular ileocolostomy, as described.
Second or postoperative step: Reopening the animal sometime later for the withdrawal of bacteria as described.

pear, both of which were absent there before the operation. Dogs 4 and 5 exhibit only a comparatively slight increase in the postoperative bacterial count. That a shift of the colonic organisms to abnormally higher levels in the ileum occurs after elimination of the natural ileocecal valve by the usual "short-circuiting" operation is indicated by animals 3 and 5.

Table II embodies the results of the bacteriological examination after the introduction of a valve with the ileocolostomy; this series of dogs shows in general that the bacterial flora either remains unchanged from the normal, or even is reduced, which indicates a favorable effect of the inclusion of the valve. In comparison with the preoperative state, dog 1, for instance, reveals no appreciable bacterial change, 14 days after the operation, in the entire stretch of ileum examined. Dogs 2, 3, 4, 5, and 6 manifest a variable reduction in bacterial counts after operation. Even a small shift of the Bacillus coli organism toward the colon is seen in dogs 2 and 5, an observation which is as favorable a point for the valvular ileocolostomy as the shift in the opposite direction is an unfavorable point for the ordinary ileocolostomy.

In addition to the bacteriological study, general observations of the condition of the animals —appearance, frequency of defecation, type of stool, etc.—after the operations furnished some measure of the relative effects of the two types of ileocolostomy. Of 14 dogs, which were subjected to the ordinary type of ileocolostomy, almost all of them had increased number of bowel move-

ments, liquid stools, and as a consequence the appearance and symptoms of dehydration. On the other hand, the dogs in which a newly constructed valve was added to the ileocolostomy showed an appearance and conditions of defecation which deviated little from the normal state.

SUMMARY AND CONCLUSION

The present paper describes a surgical method which utilizes a segment of the intestine for the formation of an "artificial ileocecal valve" that resembles the normal ileocecal valve grossly, histologically, and physiologically. By the addition of such a valve to an ileocolostomy, the attempt is made to reconstruct the normal anatomy as closely as possible.

A preliminary bacteriological study revealed that the bacterial flora in the ileum of a dog after a valvular ileocolostomy was performed remained essentially unchanged, and in some instances even showed a smaller number of organisms. This result is in contrast to the findings in cases of ordinary ileocolostomy in which greater numbers of organisms were isolated, and at intestinal levels higher than occurred normally.

Comparison of the general state of the animals after ordinary ileocolostomy with that of animals after valvular ileocolostomy also furnishes evidence that the second or new procedure leaves the animal in a better condition physiologically than the first.

The conclusion is warranted that the introduction of a valve of this kind in ileocolostomies in man can be recommended in surgery.

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TREATMENT OF OBSTRUCTIVE HYDROCEPHALUS IN ADULTS

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SURGICAL procedures for the relief of hydrocephalus fall into three principal categories. They are carried out for: (1) removal of the cause of obstruction; (2) reduction of the output of cerebrospinal fluid; (3) establishment of a new channel to permit the spinal fluid to escape from the ventricular system and reach the areas of absorption in the subarachnoid space. Methods of removing lesions which block the third and fourth ventricles or compress the sylvian aqueduct are already well known and therefore do not come under the subject discussed in this report. Treatment of the communicating type of hydrocephalus also constitutes a special problem quite separate from the conditions included herein. The type of hydrocephalus which we wish to discuss is produced by inoperable tumors in the region of the third and fourth ventricles or the intervening aqueduct and the still rarer benign occlusions of the aqueduct of Sylvius. Patients with this condition suffer from severe headaches and vomiting, progressive loss of vision from papilledema, and terminal failure of the intracranial circulation and respiratory paralysis.

In the past, treatment of hydrocephalus caused by inoperable tumors has been discouraging, but in recent years two methods of establishing free and lasting drainage of the ventricular system into the subarachnoid space have been described. Five years ago Stookey and Scarff advocated opening the anterior and posterior walls of the third ventricle and permitting the obstructed cerebrospinal fluid to escape into the large suprachiasmatic and interpeduncular cisterns. This operation had already been described by Dandy (3), but his exposure usually necessitated cutting one optic nerve and his results in young children have been unsatisfactory as we shall note. It was also performed by Cushing in at least one patient and the operation was illustrated in a sketch. The results are not mentioned, but the Peter Bent Brigham Hospital records state that 2 years later the patient remained relieved of her obstructive hydrocephalus and had recovered nearly normal vision. In 1939 Torkildsen described an alternative method of shortcircuiting the flow of spinal fluid from one of the lateral ventricles into the cisterna magna by means of a rubber catheter. After the standard suboccipital craniectomy and the discovery of an inoperable obstructing lesion, this procedure is carried out by placing one end of a catheter in the posterior horn of one of the lateral ventricles through an occipital burr hole and then passing the other under the galea and scalp so that it can be fixed in the cisterna magna.

Either method is capable of establishing lasting drainage. Each operation has certain advantages, and both are far superior to older methods, which have never been really satisfactory. These procedures and the reasons for their failure should be briefly mentioned. Suboccipital decompression has rarely relieved the pressure on an obstructed aqueduct sufficiently to permit free drainage, and then for only a brief period. Passage of a catheter through the compressed aqueduct, with a length of buried rubber tubing left in place to keep the channel between the third and fourth ventricles open has occasionally been successful (Dandy, 2).[1] In view of the frequent distortion and obliteration of the aqueduct, the passage of a catheter up into the third ventricle often involves forcing a passage blindly through the surrounding structures of the mesencephalon. According to Dandy (3) the older method of puncturing the corpus callosum to drain the lateral ventricle always failed because the opening in the ventricular roof remains patent for but a short time. The same has been true of attempts to drain the lateral ventricles directly into the subarachnoid space over the convexity of the hemisphere. Even if these openings in the brain substance were to remain open, the arachnoid would become adherent at their edges so that spinal fluid could not enter the general subarachnoid space. Coagulation of the choroid plexus (Putnam), which occasionally permits the destruction of a sufficient amount of the plexus in infants with hugely dilated ventricles, is not satisfactory in adults with less extreme degrees of hydrocepha-

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[1] In a subsequent article Dandy (3) stated that "strictures of the aqueduct of Sylvius recur after any attempt to restore the lumen." In Dandy's reported cases he subsequently removed the buried section of catheter. Dr. W. J. Mixter in this hospital has left the tubing in place in a single case with at least partial relief (unpublished data).

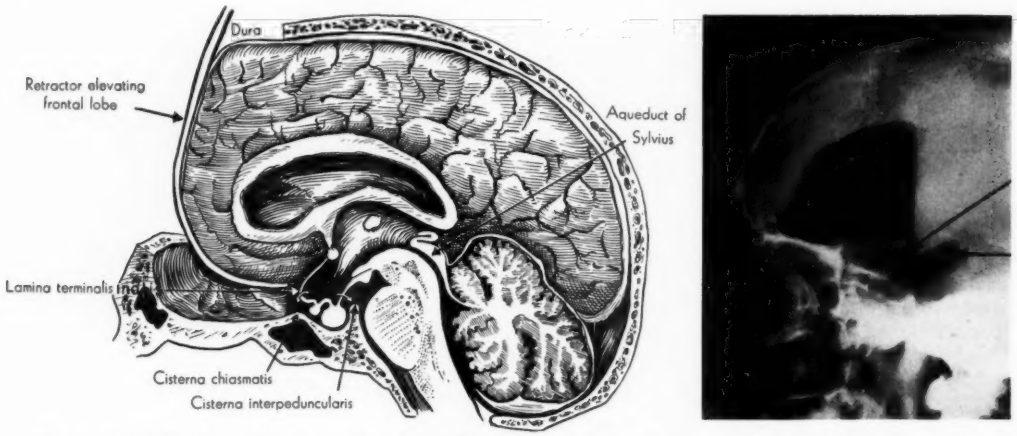

Fig. 1. a, left, Right transfrontal craniotomy and elevation of frontal lobe exposes bulging, paper-thin lamina terminalis of the dilated third ventricle. This is opened widely under direct vision. A second posterior perforation may be made into the interpeduncular cistern with a bent wire probe through the posterior floor of the ventricle. The latter procedure is not absolutely essential and was carried out only in the first case. (Reproduced from article by White. Courtesy *The Yale Journal of Biology and Medicine.*) b, right, Pre-operative ventriculogram in Case 3. The left hand arrow marks the air shadow in the anterior third ventricle where the lamina terminalis is opened; upper right arrow, third ventricle; lower right arrow, tip of temporal horn.

lus. The same is true of Dandy's (4) method of resecting the choroid plexus. Although occasional successful results may have been achieved by these methods, none of them has proved consistently satisfactory. In contrast with these discouraging results, experience with the two new procedures to be summarized has been gratifying.

SUPRACHIASMATIC DRAINAGE OF THE THIRD VENTRICLE THROUGH THE LAMINA TERMINALIS

In 1922 W. J. Mixter successfully punctured the floor of the third ventricle in a hydrocephalic infant after inserting an operating cystoscope through the anterior fontanelle, dilated lateral ventricle, and foramen of Monro. According to the hospital records this infant appeared to do well for a few weeks and then died suddenly. No postmortem examination was obtained, but it seems probable that death was due to closure of the stoma. In the same year Dandy (3) reported opening the dilated anterior wall of the hydrocephalic third ventricle in 6 children. He did not report late results, but has informed us in a letter that he has given it up because "external" hydrocephalus (from collection of fluid in the subdural space) regularly followed. For this reason he subsequently advocated making a stoma in the lateral and posterior wall of the third ventricle through a lateral approach under the temporal lobe (5) in order to secure drainage into the larger interpeduncular cisterns. When Stookey and Scarff, 5 years ago, reported their experience in adults with ventriculostomy through the anterior and posterior walls of the third ventricle they found their results highly satisfactory. In the past 2½ years we have drained the ventricular system in this manner in 11 cases, in 10 of which an opening was made in the lamina terminalis only. The chiasmatic cistern in the adult is of sufficient depth so that the surrounding arachnoid is not likely to become adherent over the opening. External hydrocephalus, reported by Dandy in children, has not been a complicating factor. That an opening in this region may effectively drain the obstructed ventricles over a period of years is proved by a case reported by Sweet from the Billings Hospital in Chicago.

In this patient, a middle-aged woman, signs of an obstructive hydrocephalus developed suddenly in 1925. She was confined to bed for the next 4 weeks with severe headaches, vomiting, and diplopia. In addition she showed a progressive failure of memory, disturbance in gait, a left-sided paresis of the seventh, tenth, and twelfth cranial nerves, and irregular pupils which did not react well to light. All of these signs and symptoms cleared up spontaneously within 4 months, and she remained well for over 9 years. In 1935 signs of brain-stem and cerebellar pathology reappeared, but without any increase in intracranial pressure. Death occurred within a few months from bronchopneumonia and acute pulmonary edema. At postmortem examination the primary lesion was found to be an enormous teratoid tumor of the cerebellum, which had obliterated the sylvian aqueduct, but caused only a moderate hydrocephalus. The explanation of the patient's ability to survive this long standing obstruction was found to lie

in the drainage of the ventricular system through an opening in the lamina terminalis. This must have ruptured spontaneously 11 years before, and the case constitutes the longest clinical demonstration on record of the efficacy of third ventriculostomy for the relief of obstructive hydrocephalus.

An exactly similar opening can be made surgically in the paper-thin bulging wall of the third ventricle above the optic chiasm. The operation differs little from the usual method of dealing with a suprasellar cyst. Stookey and Scarff have given a clear account of the procedure, and a preliminary report on 3 cases has been published by White (13). A moderate sized frontoparietal bone flap is turned down on the right side, as in the exposure of a pituitary tumor. The anterior sawcut should be placed as low down on the forehead as possible without opening the frontal sinus. If the dura is tense, the anterior horn of the ventricle should be tapped before proceeding further. The dura of the anterior fossa is then elevated and opened well back, in order to protect the cortex as the frontal lobe is elevated (Fig. 1a). Within the dura the use of a lighted retractor and wide development of the anatomical landmarks, with exposure of both optic nerves, permit a clear view of the optic chiasm. In cases of extensive hydrocephalus, the lamina terminalis bulges just above the chiasm as a paper-thin semitransparent membrane (Fig. 1b). This and the thin film of overlying arachnoid are easily punctured, and, after aspiration of cerebrospinal fluid, the frontal lobe collapses sufficiently to permit a wide exposure. At this stage the entire chiasm including a centimeter or more of the optic tracts, the anterior cerebral arteries, and both internal carotids become clearly visible. The membrane can then be punctured and widely opened by spreading with an alligator forceps, and its thin edges teased away with a pituitary rongeur. By removing the membrane from above the chiasm and out to the optic tract on either side it is possible to create an opening 1 to 2 centimeters in diameter. The operator can then see well up inside the dilated third ventricle, so that one of us (White, 14) has been able to carry out a series of stimulation experiments on the sympathetic hypothalamic nuclei which lie in the lateral ventricular wall with a bipolar electrode. Stookey and Scarff recommended that in addition to opening the lamina terminalis a perforation be made through the posterior portion of the floor of the third ventricle to establish drainage into the interpeduncular cistern. This can be done with a bent probe, but cannot be carried out under direct vision. This maneuver gives added protection against recurrence and should therefore be carried out when it can be done easily. We have, however, made such a secondary stoma only in the first case and have come to feel that a wide anterior drainage opening into the suprachiasmatic cistern is sufficient.

Fig. 2. Third ventriculostomy stoma in Case 2 at postmortem 6 weeks after operation. The right optic nerve is drawn downward by a thread to show the wide opening into the third ventricle above the chiasm. (Reproduced from article by White, courtesy of *The Yale Journal of Biology and Medicine*.)

Closure of the wound should not be undertaken until every precaution has been taken to assure hemostasis. With the relief of obstructive hydrocephalus, the brain is shrunken and postoperative bleeding is therefore a serious risk. In spite of the greatest care, hematomas developed in Cases 5 and 6 which were a contributory cause of death.

The case reported by Sweet and cited here is evidence that a wide stoma through the lamina terminalis will stay open for years and provide a satisfactory channel for the escape of spinal fluid from the obstructed ventricles into the suprachiasmatic cistern and its distribution and absorption in the subarachnoid space. One case reported by Stookey and Scarff had been relieved for 3 years, and our first patient remains perfectly well at the end of 2½ years.

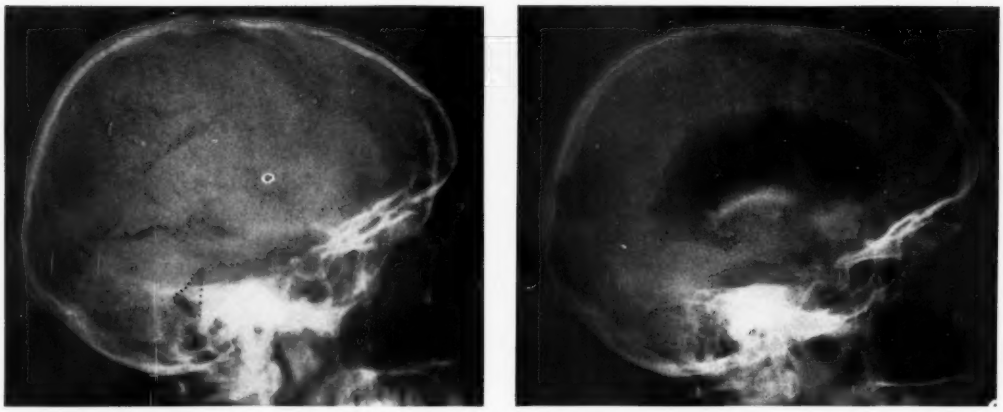

Fig. 3. Air studies in Case 1. a, left, Encephalogram illustrates a normal fourth ventricle with obstruction of the aqueduct, which is outlined by dots. b, Ventriculogram shows enlargement of lateral and third ventricles. The upper end of the aqueduct ends in a bulbous dilation at tip of arrow (brought out by dotted line).

Figure 2, a photograph taken postmortem in Case 2, illustrates a wide open stoma 7 weeks after operation. In the 3 other adult cases in which postmortem examinations were performed the stoma was found to be patent and draining successfully in every instance. A subdural fluid collection, as reported by Dandy in his cases, was seen in a single case of infantile hydrocephalus which is not included in this report, but postmortem examination in the 4 cases here described showed that the spinal fluid was confined to the subarachnoid space and was being effectively absorbed.

Our 11 patients suffered from a variety of conditions ranging from apparently benign obstructions of the sylvian aqueduct to tumors which arose in the region of the third ventricle, brainstem, and cerebellum (Table I). Of these patients 2 have regained useful vision and are alive and well 2½ years to 15 months after operation (Cases 1 and 9). When last heard from these patients were leading normal lives. The most dramatic result was obtained in the first case:

Case 1. Mrs. L. S., aged 30 years, had noticed headaches of increasing severity for three years, and in addition a rapid loss of vision over a period of 2½ months. Examination on admission showed papilledema of 3 diopters with retinal hemorrhages, and visual acuity reduced to 2/200 in the right eye and 20/50 in the left. The neurological examination was normal. As her spinal fluid pressure was below 200, a pneumoencephalogram was performed and showed a clear-cut block of the sylvian aqueduct just above the fourth ventricle (Fig. 3a). A subsequent ventriculogram demonstrated marked dilatation of the lateral and third ventricles, with the aqueduct ending in a bulbous dilatation a centimeter below the pineal body (Fig. 3b). The long history of headaches and the appearance of the block in the x-ray films strongly suggested a benign occlusion of the sylvian aqueduct. Third ventriculostomy by the suprachiasmatic route was therefore carried out on March 12, 1938. The following is an excerpt from the operative note:

After the usual right frontal craniotomy, the dura along the floor of the anterior fossa was elevated and opened well back toward the sphenoid ridge. Tapping of the ventricle relieved the tension of the brain and thereafter it was easy to free up the entire optic chiasm and both optic nerves, as well as to expose the region just above the chiasm and the internal carotid, middle, and anterior cerebral arteries on the right. With these landmarks well in view, the bluish thinned-out shell of the third ventricle just above the chiasm was perforated. A large amount of ventricular fluid escaped. This opening was enlarged until it was nearly 1 centimeter across. Finally a puncture was made in the posterior floor of the third ventricle. It could be felt when the tip of the silver probe went through the posterior wall and entered the interpeduncular cistern. This part of the operation was bloodless. After adequate hemostasis had been established the dura, bone, and scalp were resutured in the usual manner.

The patient made a most satisfactory recovery and was discharged after 19 days. During this short period her papilledema had receded to a striking degree. Within a period of 5 weeks the patient's visual acuity had recovered to 20/70 in the right eye and 20/25 in the left. When seen again 2 months later visual acuity remained the same. Both optic discs were flat, but marked atrophy persisted on the right. Since this visit the patient has reported on numerous occasions by letter, stating that she remains free from headaches, has retained useful vision, and is able to lead a normal life. The last report was received on November 14, 1940, 2 years and 8 months after her operation.

Four other patients (Cases 4, 7, 8, and 11) were relieved of hydrocephalus. The first 2 of these were unfortunately operated upon too late to save vision. The third died 2 months later in another hospital of bronchopneumonia and permission to perform a postmortem could not be obtained. The fourth was the only patient who

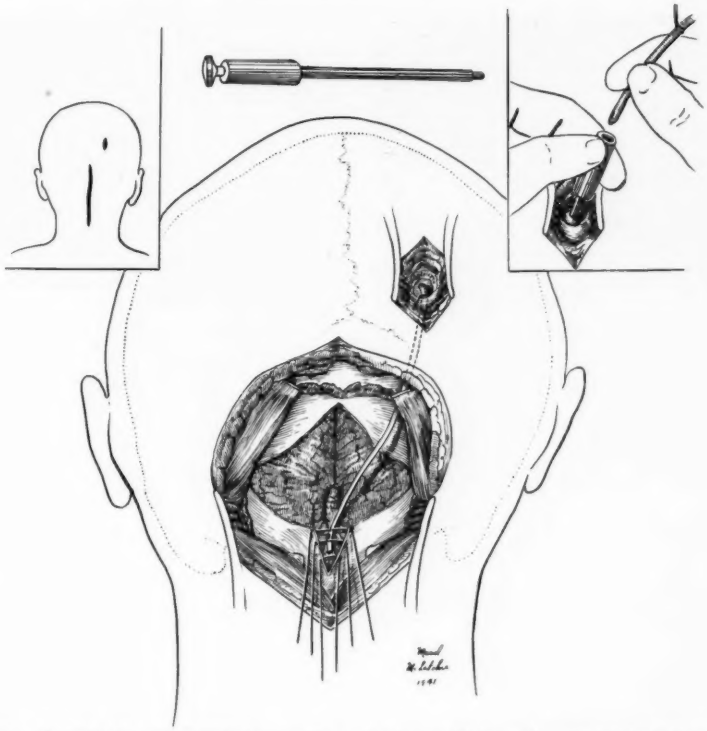

Fig. 4. Technique of Torkildsen ventriculostomy. The inserts illustrate incisions for the suboccipital craniotomy and insertion of catheter in right lateral ventricle (upper left); the trocar for inserting catheter into the ventricle (upper center). Technique of inserting the catheter. Note the thread that has been tied to the catheter to serve as depth marker and to suture to the galea after the trocar has been withdrawn (upper right). In the main drawing the stitches are shown which are used for anchoring the lower end of the catheter into the cisterna magna and closing the dura. The arachnoid covering the cisterna has not been sketched, but it is important to include this membrane in the sutures in addition, as the description in the text indicates.

failed to show a reduction in intracranial pressure to a normal level. This was due to a large cavernous hemangioma of her left temporoparietal lobe with extension to the basal ganglia. This tumor not only compressed the aqueduct, but raised the intracranial pressure by its great size. A subsequent partial removal of the mass resulted in the patient's death.

Three patients died as a result of operation, making a case mortality of 27 per cent. These included Case 3 in which patient died of pulmonary embolism, and Cases 5 and 6, in which patients developed complicating postoperative hematomas. Death in Cases 2 and 10 was due to compression of vital centers by the tumor, which continued after the obstructing hydrocephalus had been relieved.

Before Torkildsen reported his ingenious operation we drained the obstructed ventricular system through the anterior route in cases in which a previous posterior exploration or strong clinical and ventriculographic evidence pointed to an inoperable lesion as the cause of the obstruction. But the bitter experience of missing a cystic hemangioblastoma of the cerebellum in Case 2, in which air injection had indicated a tumor of the midbrain, taught us the risk of relying on ventriculographic evidence for the exclusion of an operable lesion in the posterior fossa.

CASE 2. H. S., a 6 year old girl, entered the Children's Service after 10 months of headache and vomiting. She had a bilateral sixth nerve paresis, with spastic weakness of her left leg and arm, as well as of the right leg. At first there was only slight papilledema and no nystagmus or signs of cerebellar pathology. Her pupils reacted very sluggishly both to light and accommodation. Flat skull plates showed increased convolutional markings and widened cranial sutures. On the supposition that these symptoms and signs were due to occlusion of the fourth ventricle by a medulloblastoma, a trial of radiation therapy was in-

Fig. 5. Postoperative ventriculogram with catheter in position.

stituted and continued for several weeks, but without any improvement.[1]

The girl was first seen in consultation by one of us (J. C. W.) at the end of this period. She was then semistuporous and in too poor condition for a satisfactory neurological examination. One additional observation of interest, which had not been recorded previously, was that upward movements of her eyes appeared to be limited. A ventriculogram was performed and suggested obstruction of the aqueduct near its upper end, "probably due to a tumor which lies mainly at the floor of the aqueduct." As we believed that a tumor in this situation was inoperable, anterior drainage of the third ventricle was performed through a suprachiasmatic approach on August 12, 1938.

Following operation the patient made a surprisingly good recovery and regained the use of her extremities. The signs of increased intracranial pressure disappeared. When the left ventricle was tapped only 40 cubic centimeters of xanthochromic fluid escaped at normal pressure, whereas before operation the pressure had been over 400 millimeters. But in spite of the relief of the obstructive hydrocephalus she began to develop signs of cerebellar pathology a month later, with evidence of compression of the vital medullary centers, which caused her death within 3 weeks.

Postmortem examination revealed satisfactory relief of hydrocephalus, with a wide open stoma through the lamina terminalis above the optic chiasm (Fig. 2). Comparison of the preoperative ventriculogram with postoperative measurements of the ventricles showed a striking reduction in their size. The cause of death was bilateral bronchopneumonia, secondary to compression of the brain stem by a cystic hemangioblastoma of the left cerebellar hemisphere. The primary lesion could have been easily attacked and the compression of the aqueduct relieved if a suboccipital exploration had been made soon after her admission.

As a result of this unfortunate experience we have reached the conclusion that ventriculostomy through the anterior wall of the third ventricle should not be performed unless both clinical and laboratory evidence point unquestionably to the presence of an obstructing lesion which is inoperable because of its situation, or unless this diagnosis has been established at a previous exploration. Under these circumstances, as in Cases 1, 3, 4, 5, 6, 10, and 11, this form of ventriculostomy would seem to be the most satisfactory operation. Had we known of Torkildsen's approach sooner, we should have preferred this in Cases 2, 7, and 9, in which the cause of obstruction was uncertain. This valuable procedure, as will be seen, permits the surgeon to explore the posterior fossa as a preliminary to permanent ventricular drainage. In Case 8 with otitic hydrocephalus an occipital operation could not have been considered in any case because of the presence of a septic mastoid wound.

[1]Following the mistaken diagnosis in this patient, no further patients have been submitted to therapeutic trial of radiation for medulloblastoma without previous verification by exploration and biopsy.

DRAINAGE OF LATERAL VENTRICLE INTO THE CISTERNA MAGNA—TORKILDSEN OPERATION

A standard suboccipital craniectomy is performed through a midline longitudinal incision in the scalp and upper neck. If the cervical fascia is cross-cut just below its insertion in the occipital bone, there is no need to make a cross-bow incision in the scalp. After scraping the muscles off the bone low enough to expose the arch of the atlas vertebra, this portion of the occiput and the arch of the atlas are rongeured away. The dura is next opened crucially. In opening the arachnoid over the cisterna magna it is important to incise it longitudinally and then to use every precaution to preserve the two lateral flaps of arachnoid and dura intact, so that the cistern can be reconstructed in the subsequent closure. The surgeon is then in a position to make a thorough exploration of the posterior fossa and also to test the patency of the aqueduct by determining whether it will admit the passage of a fine soft rubber catheter. In the face of an inoperable high tumor or an occlusion of the aqueduct Torkildsen recommended the following procedure. If an occipital burr hole for decompression of the ventricular system has not been made as a preliminary to opening the tense cerebellar dura, a small trephine opening is made in the occipital bone 3 centimeters above the tentorium and directly over the posterior horn of the right lateral ventricle. The position of the posterior horn is first ascertained by puncture. As the ventricular needle is withdrawn a trocar 4 millimeters in diameter is inserted along its tract. When the stylet is pulled out the metal sleeve serves as a guide for insertion of a No. 8 soft rubber catheter. Before this is slipped into the ventricle an extra eye should be cut close to its tip and a silk ligature tied around it to serve as a depth marker and for later suture

of the catheter to the galea at its point of exit from the skull. The catheter tip should be thrust 2 to 3 centimeters into the ventricular cavity. The metal sleeve is then removed and the rubber tube sutured firmly to the galea. When this maneuver has been completed, a tunnel is made between the galea and cranium to permit the passage of the catheter from the small separate incision over the trephine opening to the larger midoccipital one. This can be carried out without difficulty by separating the tissues with a large curved hemostat, seizing the lower end of the catheter, and drawing it back through the resultant tunnel. The catheter is now cut off so that its lower end just reaches the cisterna magna (Fig. 4). This is then reconstructed as accurately as possible over the tube by suturing together the two lateral flaps which were saved for this purpose. Burying and securely fixing the end of the catheter beneath the arachnoid is perhaps the most important part of the operation. It can be accomplished best if the surgeon plans his incision carefully as he opens the dura and arachnoid overlying the cistern. In reconstructing these membranes we have passed fine silk stitches through the dura, arachnoid, and outer layer of catheter, and then out through the same layers in reverse order. Both incisions are then closed in layers with silk sutures. When the dressing is applied a checkrein of adhesive tape is incorporated in it from vertex to shoulder blades to prevent forward flexion of the head for the first few days. Figure 5 illustrates the position of the catheter in the first patient, with the ventricles outlined by air injection 12 days after operation.

The three adult patients who have been submitted to this operation in the advanced stage of hydrocephalus with intense headache, vomiting, high grade papilledema, and increasing somnolence have recovered and remained relieved of their obstructive symptoms for periods ranging from 5 to 18 months. The striking improvement which may follow the institution of permanent drainage by a buried catheter is summarized in Table II and in the history of the following patient:

CASE 13. T. K., a 21 year old man, entered the hospital with a 10 months' history of headache, chiefly in the occipital region. Three weeks before admission his headaches had become increasingly severe and incapacitating. For several days before entry he held his head rigid because of the pain, but he was able to walk without apparent unsteadiness. He complained of episodes of nausea but had not vomited. Recently his family had noticed increasing irritability and slowing of his speech, but no definite change in his mentality.

On examination the patient was sluggish mentally and held his neck in slight extension. His breathing was slow and labored. Ophthalmoscopic examination revealed 4 to 5 diopters of choking, with small striate hemorrhages above both discs and a small hemorrhage in the right macula. His vision was very poor, particularly in the right eye, and the rough field determinations were normal, but his condition was too critical to permit accurate examination. There were no outstanding cerebellar signs and no nystagmus, but a suggestive impairment in upward deviation of the eyes. Otherwise the cranial nerves were normal. This was also true of the spinal reflexes as well as of the motor and sensory examinations.

Because of threatened respiratory paralysis, occipital burr holes were made on the evening of his admission. The next morning a cerebellar exploration was performed with Torkildsen drainage of his right lateral ventricle into the cisterna magna. The operative note reads as follows:

"Under general anesthesia a ventricular needle was inserted through the right-sided burr hole made last night. The ventricle was easily entered and proved to be large, containing over 75 cubic centimeters of fluid under high pressure (200+). This having been ascertained, the safest course appeared to be a cerebellar exploration and palliative drainage of the hydrocephalus, if no operable tumor were found. The patient was therefore placed in cerebellar position, and through a midline incision the occipital muscles were cross-cut and a broad area of occiput was exposed. This was removed together with the arch of the atlas. After the dura had been opened, the cerebellar hemispheres were seen to be symmetrical and the vermis not widened. Only a small pressure cone was present. The cerebellum was not tense because the needle had been left in the lateral ventricle. After separation of the cerebellar tonsils one could look upward into a normal appearing fourth ventricle. A No. 10 catheter slipped up the aqueduct met a definite obstruction at a point 4 to 5 centimeters above the lower end of the fourth ventricle. When the anesthetist gave jugular compression, no fluid escaped from above, suggesting that the site of obstruction lay in the upper portion of the aqueduct in the region of the quadrigeminal plate, and that it would be inaccessible to surgery from below. Therefore the palliative procedure described by Torkildsen was carried out. The tip of a No. 8 catheter was buried in the posterior horn of the ventricle and the tube was then passed underneath the scalp from the incision over the burr hole to the median cerebellar incision. Its other end was carefully sutured beneath the arachnoid and dura in the cisterna magna. We were very careful to ascertain that spinal fluid flowed freely out of the tube before closing the arachnoid and dura. The neck muscles were then carefully resutured to the occiput and to each other in the midline. This procedure was tolerated well, blood pressure remaining at a normal level throughout."

The patient was in good condition after operation, and on the fourth day his lumbar and intraventricular pressure readings were normal. Phenolsulfonphthalein was injected into the ventricle and 10 per cent recovered in the urine in the next 2 hours. A ventriculogram carried out 3 weeks later showed free drainage from the previously obstructed ventricles, as all the gas was found distributed over the subarachnoid space. Five days afterward a second ventriculogram was undertaken; 1 cubic centimeter of phenolsulfonphthalein was injected first, followed by 90 cubic centimeters of oxygen. The injection displaced spinal fluid from the ventricles and this was drained through a second needle in the lumbar subarachnoid space. The rapid appearance of dye in the fluid recovered in the lumbar region and a previous pressure reading of 105 millimeters established the patency of the artificial drainage system. The subsequent x-ray films showed a symmetrical dilatation of the lateral and third ventricles withou any visible filling of the aqueduct. Beginning on the twenty-fifth postoperative

TABLE I. RESULTS OF THIRD VENTRICULOSTOMY THROUGH THE LAMINA TERMINALIS IN THE TREATMENT OF OBSTRUCTIVE HYDROCEPHALUS

Case	Symptoms	Neurological examination	Optic discs	Vision	Cerebrospinal fluid pressure	X-ray	Diagnosis	Operation	End-result
No. 1 Louise S. 107838 Age 30	Intermittent attacks of headache and dimness of vision, 3 yrs.	Insignificant reflex changes	Papilledema 6 D.	O.D. Nil O.S. Faulty light perception	170	Obstruction of aqueduct with internal hydrocephalus	Obstruction of sylvian aqueduct	3rd ventriculostomy	Leads normal life for 2½ years. Recovered vision 20/70, 20/30
No. 2 Hilda S. 138709 Age 6	Headache and vomiting, 9–10 mos.	Bilateral spastic weakness. L. VI nerve paralysis	Papilledema 4 D.	Greatly reduced	450	Obstruction aqueduct, upper end	Hemangioblastoma of the cerebellum (postmortem)	3rd ventriculostomy	Relief of hydrocephalus but died of medullary compression after 6 wks.
No. 3 Vincent G. 103089 Age 20	Headache and vomiting, 15 mos. Attacks of unconsciousness with rigid extension of extremities, 2 mos.	Dulness, obesity with striae, bilateral ptosis, no reaction of pupils, limited upward gaze, bilateral pyramidal signs	Bilateral blurring	Impossible to test	430	Pineal calcified, displaced backward and downward. Hydrocephalus. No air in aqueduct and 4th ventricle	Pinealoma (postmortem)	3rd ventriculostomy	Relief from headache, cerebrospinal fluid pressure decreased. Died 13 days after operation from thrombophlebitis of femoral vein and pulmonary embolism
No. 4 Theodore K. 126822 Age 24	Almost blind since birth, less vision and occipital headache last 9 mos.	Chorioretinitis. Insignificant and inconsistent reflex and sensory changes	Papilledema 3 D.	Very poor	300	Dilatation of lateral ventricles and 3rd ventricle. Aqueduct and 4th ventricle not seen	Obstruction of sylvian aqueduct	1. Cerebellar exploration 2. 3rd ventriculostomy	Relief from headache, cerebrospinal fluid pressure lower. At 3 mos. vision improving
No. 5 Charles Sm. 124277 Age 35	Headache and vomiting, 14 mos. Unsteadiness of gait, awkwardness of hand	Wide-based gait, swaying to both sides, ataxia, and bilateral adiadokokinesis	Papilledema 2 D.	20/100 20/100	380	Increased blood vessel markings. Dilatation 3rd and both lateral ventricles. Upper aqueduct filled	Tumor of 4th ventricle, papilloma of choroid plexus (postmortem)	1. Cerebellar expl. (neg.) 2. 3rd ventriculostomy 3. Evacuation postoperative hematoma	Died 24 hours after 2nd operation
No. 6 Vincent V. 181355 Age 46	Headache 6 yrs. Dizziness, bilateral tinnitus, spells of blindness, unsteadiness of gait	Unsteadiness of gait, ataxia, adiadokokinesis	Papilledema 5 D.	20/100 20/40	300	Internal hydrocephalus. Aqueduct and 4th ventricle not visualized	Cerebellar cyst	1. Partial removal of cerebellar cyst. 2. Re-exploration. 3. 3rd ventriculostomy. 4. Evacuation postoperative hematoma	Coma, hyperthermia, and death following 4th operation
No. 7 Rosella G. 200394 Age 20	Scotomas, blurring vision, intermittent numbness of face, 5 wks. Headache 3 wks.	Mental deficiency. No localizing signs	Papilledema with hemorrhages	Greatly reduced (fingers)	380	Chronic increased pressure, internal hydrocephalus, probable obliteration of posterior portion of 3rd ventricle	Brain tumor, ? involvement of posterior part of 3rd ventricle	3rd ventriculostomy	No headache, low cerebrospinal fluid pressure. Developed left sided paresis at 9 mos.
No. 8 Charles So. 198029 Age 26	Running ear 4 mos. Headache, nausea, vomiting, dizziness, and poor vision, following mastoidectomy, 3 mos.	Cloudy sensorium, L. homonymous hemianopsia, R. VI, L. VII and XII nerve weakness. Reflexes noncontributory	Papilledema 3 D.	Reduced	540	Dilatation lateral and 3rd ventricles, normal sized 4th ventricle	Obstruction of sylvian aqueduct, ? o. cerebellar abscess or arachnoiditis	3rd ventriculostomy	Temporary improvement, but died 2 mos. after operation from bronchopneumonia

TABLE I. RESULTS OF THIRD VENTRICULOSTOMY THROUGH THE LAMINA TERMINALIS IN THE TREATMENT OF OBSTRUCTIVE HYDROCEPHALUS—Continued

Case	Symptoms	Neurological examination	Optic discs	Vision	Cerebrospinal fluid pressure	X-ray	Diagnosis	Operation	End-result
No. 9 Agnes S. 188968 Age 44	Intermittent headache, vomiting, visual disturbances, ataxia, 6 yrs.	Drowsy, pupils fixed L. and A., disturbance of upward gaze, L. facial weakness, R. Babinski	Papilledema, L. > R.	20/20 20/70	270	Dilatation lateral and 3rd ventricles, no air in aqueduct or 4th ventricle	Midbrain tumor	3rd ventriculostomy	Feeling well and doing housework 15 mos. after operation. Local neurological signs slowly progressing. No papilledema. Cerebrospinal fluid pressure low
No. 10 Alma DeM. 207008 Age 16	Headache, generalized convulsions, unsteadiness, weight increase, bilateral tinnitus, choreiform movements	Obesity with striae, limited upward gaze, no reaction to light, poor convergence, slight R. facial weakness, falling backward and to left when walking	Papilledema, 2-3 D.	20/50 20/40	—	Calcified tumor in region of the pineal	Pinealoma (postmortem)	3rd ventriculostomy	Improved, but died suddenly during a course of x-ray treatment
No. 11 Mary S. 198039 Age 16	Headache and dizziness 3 weeks. Fall with confusion, exacerbation of headache, and pain between eyes, 4 days	Weakness of L. III & XII nerves, rigidity of neck, spasticity of legs, ? R. Babinski. Other reflexes noncontributory	Slight papilledema	20/200 20/200	400	Dilatation of both lateral ventricles and of 3rd ventricle, with mass protruding into L. lateral ventricle and compressing aqueduct	Cavernous hemangioma of choroid plexus	1. 3rd ventriculostomy. 2. Intraventricular exploration	Died 17 days after second operation from bronchopneumonia

TABLE II. RESULTS OF TORKILDSEN OPERATION IN THE TREATMENT OF OBSTRUCTIVE HYDROCEPHALUS

Case	Symptoms	Neurological examination	Optic discs	Vision	Cerebrospinal fluid pressure	X-ray	Diagnosis	Operation	End result
No. 12 Evelyn M. 215812 Age 32	Vomiting, intermittent occipital headache, black spots in R. eye, numbness and weakness R. leg and hand	Disturbance of conjugate eye movements, nystagmus, buzzing in both ears, hypesthesia to pinprick R. side	Papilledema, 3 D.	O.D. 20/30 O.S. 20/200	Not obtained	Postoperative ventriculogram shows obstruction high in aqueduct	Obstruction of aqueduct, ? tumor of brain stem	Exploration of posterior fossa with catheter drainage (Torkildsen)	Gradual disappearance of symptoms except for nystagmus and occasional headaches. Several series of x-ray treatments. Returned to work and leading normal life at 18 mos.
No. 13 Thomas K. 220726 Age 21	Occipital headaches, nausea, rigidity of neck, diminution of vision, irritability, and slowing of speech, 8 mos.	? Impairment upward gaze. Mentally sluggish. Head in slight extension. Breathing slow and labored	Bilateral papilledema, 4-5 D. with hemorrhages	Not tested	Not obtained	Flat plates not contributory, no preoperative air injection	Obstruction of aqueduct, ? tumor	Exploration of posterior fossa with catheter drainage (Torkildsen)	Gradual disappearance of all symptoms. Returned to work at 11 mos.
No. 14 Paul Z. 90361 Age 51	Headache and increasing difficulty with walking	Not co-operative, very drowsy, limitation of upward and lateral gaze, some disturbance of co-ordination	Papilledema	20/40 20/30	1) 85 2) 190 3) 215 Xanthochromic 90 rbc.	? Obstruction of aqueduct	Obstruction of aqueduct, ? midbrain tumor	Exploration of posterior fossa with catheter drainage (Torkildsen)	Lives a fairly normal life at home at 4 mos.

day x-ray therapy was given in six 200r doses. At the time of discharge the last traces of papilledema were disappearing, and vision had recovered to 20/40 and 20/20. There was still impairment of upward gaze, suggestive of a midbrain lesion.

Since discharge the patient has made a most satisfactory recovery. At his last follow-up examination on September 26, 1940 (11 months after operation) he appeared to be in excellent health. He complained of no headaches or other symptoms of intracranial pathology. If he stood up suddenly there was momentary unsteadiness, but otherwise his gait and movements were normal. He had recovered full upward movement of the eyes and showed no neurological abnormality. Except for slight pallor of the right optic disc, ophthalmoscopic examination showed normal conditions. The patient felt that his vision had fully recovered. He planned to return to his previous occupation as a clerk.

SELECTION OF OPERATION

Both methods of draining the obstructed ventricles here reported appear to accomplish their purpose in an effective and lasting manner. The obstructed cerebrospinal fluid is drained into the large arachnoid cisterns, whence it can be distributed to the absorbing areas in the subarachnoid space in a normal fashion. It is obvious that these procedures can be effective only in the obstructive form of hydrocephalus. In the communicating type, in which basilar cisterns or absorbing areas in the cranial subarachnoid space are obliterated, nothing can be accomplished by these operations. This variety of hydrocephalus can be diagnosed by the history of a recent meningeal infection. It can be verified by the fact that phenolsulfonphthalein injected into the ventricles appears in the lumbar region, although very little is absorbed in the blood stream and eliminated by the kidneys (Dandy and Blackfan, 6).

In choosing the most suitable method of ventricular drainage it is of great importance to localize the obstructing lesion as accurately as possible. In most cases this can be done by clinical and x-ray examination. In Case 1 a block in the sylvian aqueduct was clearly visible after the combined injection of oxygen into the lateral ventricles and lumbar subarachnoid space (Fig. 3). Pneumoencephalography, however, is often too dangerous to use in patients with elevated intracranial pressure. Ventriculography alone usually gives accurate localization in the presence of a tumor in the third ventricle, but may be misleading in infratentorial lesions. This led to an unfortunate result in the second patient, in whom an upward projection of the mesencephalon was mistaken for a midbrain tumor, whereas actually the deformity was caused by an operable cystic tumor of the cerebellum. We recommend drainage of the third ventricle only if previous exploration or the combined evidence of clinical and radiological examination has demonstrated beyond a doubt that the obstructive lesion cannot be attacked directly.

The method of Torkildsen has the strategic advantage of permitting preliminary exploration of the posterior fossa before the institution of palliative drainage of the obstructed cerebrospinal fluid. It is surprising that the presence of a rubber catheter embedded in the cisterna magna is not followed by rapid closure of its open end by arachnoid adhesions. Fortunately this has not proved to be the case, as shown by Torkildsen's experience and the long-standing relief in the 3 cases here reported. Although unlikely, it is still possible for occlusion to occur or for the rubber to deteriorate after a number of years. Should either of these complications take place, drainage can again be re-established through the suprachiasmatic route. This operation does not involve the insertion of a foreign body and appears to be a more physiological procedure in cases in which, in the posterior portion of the third ventricle or below, there is an obstruction which cannot be corrected surgically.

SUMMARY AND CONCLUSIONS

1. Two effective operations have been reported in recent years for the drainage of the ventricular system in cases of obstructive hydrocephalus in adults.

2. The first method consists of perforating the thin, bulging anterior wall of the third ventricle (lamina terminalis) and establishing drainage of the obstructed cerebrospinal fluid into the chiasmatic cistern. In certain cases it is also possible to perforate the floor of the dilated third ventricle posteriorly, thereby creating a second drainage channel into the interpeduncular cistern. From our experience we believe that this additional opening is not essential and should not be attempted unless it can be carried out with ease and safety.

3. In the second method, which is carried out only after exploration of the posterior fossa has revealed an inoperable lesion, the cerebrospinal fluid is short-circuited past the obstruction in the aqueduct, third or fourth ventricle by means of a buried rubber catheter. The tip of the catheter is inserted through an occipital trephine opening and fixed in the posterior horn of the lateral ventricle. The rubber tube is then passed beneath the scalp to the cerebellar incision and its lower end is buried in the cisterna magna.

4. As the latter operation permits a preliminary exploration of the posterior fossa, it is the more

effective method of dealing with cases of hydrocephalus in which the cause of obstruction may be an operable tumor situated in the cerebellum or fourth ventricle, or an arachnoiditis which blocks the outflow of cerebrospinal fluid. On the other hand, when the obstruction is known to be inoperable and is situated in the posterior portion of the third ventricle or caudal to this point, anterior drainage through the lamina terminalis is the more satisfactory operation.

5. Both methods are capable of producing a long lasting channel for escape of the obstructed cerebrospinal fluid into the subarachnoid space, with relief from the symptoms of elevated intracranial pressure and its dangers to life and vision. This is exemplified by the case histories of 14 patients whom we have treated in this way. The hydrocephalus has been relieved in all. Life has been preserved in 7 and useful vision has been established in 5; 4 have been able to return to work and remain in good condition after intervals of 18 months to 3 years.

ADDENDUM

Since this manuscript was sent in for publication we have received reports from Dr. F. D. Ingraham and Dr. W. J. German of 3 other patients with obstructive hydrocephalus on whom the Torkildsen operation was performed. These cases are so instructive that brief résumés of their histories have been added. We wish to thank these surgeons for their kindness in permitting us to include this interesting material.

1. A girl of 5 entered the Children's Hospital with a story of high intracranial pressure and cerebellar signs. In the course of study it was shown that she had a block at the upper end of the aqueduct. Dr. Ingraham reports that he "explored this region by dividing the tentorium and exposed a medulloblastoma. A small piece of tissue only was removed for section, and when the diagnosis was verified she was given a course of radiation. The division of the tentorium and the effects of the radiation were not sufficient to relieve the block, and a Torkildsen procedure was carried out. This patient died 14 months after this last operation. There is no question but that the bypass restored her to comparatively good health and gave her a much more satisfactory survival period than she would have had otherwise. We have now had an opportunity to study the brain and the local examination was extremely interesting. The tube was quite unchanged in appearance. It was patent and there was a reservoir at the lower end into which fluid was obviously passing from the ventricle. Death was presumably due to local increase in size of the tumor which made it impossible for fluid to pass from the cisterna magna into the subarachnoid area over the cortex."

2. Dr. Ingraham's second patient was a boy 6 years of age with a typical midline cerebellar syndrome and obstructive hydrocephalus. "At operation he was found to have a block in the aqueduct, although no tumor was exposed, and it was taken to be a congenital abnormality. The Torkildsen procedure was carried out and he was watched for 3 months. His pressure remained normal during that time, and after a short trial of clamping the tube through a small incision we thought that he might have stabilized and removed the tube. In a very short time his pressure was elevated again and the tube was replaced. For several months he had a rather large collection of fluid in the region of his suboccipital decompression. This has returned to normal contour and his pressure has stayed within normal limits. The total period of observation in this patient is also 14 months. He is now symptom free, goes to school, and takes part in ordinary activities."

3. Dr. German has written us about a patient in the New Haven Hospital on whom he performed a Torkildsen operation for stenosis of the sylvian aqueduct. This girl did not maintain lasting relief of her internal hydrocephalus so that 5 weeks later it became necessary to re-explore her posterior fossa. The lower end of the catheter opened into a large smooth walled cavity in the occipital region which was completely walled off from the cisterna magna. After further exploration of the upper end of the fourth ventricle Dr. German discovered a stenotic band at the lower end of the aqueduct, which he was able to cut and thereby released the obstruction.

This is the only case to our knowledge followed by secondary closure of the catheter. As we have pointed out in the article, such a complication can be corrected if necessary by a subsequent third ventriculostomy. It is better to run the risk of an occasional late closure of the tube than to lose the opportunity for a direct attack on an operable lesion through failure to explore the posterior fossa, as is the case when third ventriculostomy is done as a primary procedure.

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FINE ALLOY STEEL WIRE SUTURES

An Experimental and Clinical Study

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OF the many factors influencing the healing of surgical wounds, the reaction accompanying the use of different suture materials has been studied most extensively. The ideal suture, however, is yet to be found, although catgut and silk have been employed most frequently. The superiority of the latter over the former in most circumstances has been adequately demonstrated by many experimental and clinical observations (6, 7, 9, 10, 12, 13, 14, 15). However, in the presence of infection, the silk suture may act as a nidus for the organisms and prolong the period of healing. For this reason, many surgeons still prefer catgut and even the most ardent advocates of silk (6, 7, 14) warn against its use in infected wounds. In 1934, Babcock (1) proposed the use of fine alloy steel wire as a permanent suture material. Because of its fine caliber, smooth surface, nonpermeability, and chemically stable nature, he claimed that this material was satisfactory for use in both aseptic and infected wounds. This author's subsequent experience seemed to substantiate these claims (2, 3, 4). Also, Kaufman, Johnson, and Lesser, in an analysis of 56 cases of hernioplasty, found the incidence of wound infection to be much lower in the group of cases in which wire sutures were employed than in the groups closed with catgut or silk. Bunnell reported favorable results from the use of wire sutures in the repair of tendons. Preston demonstrated experimentally in rats that wounds sutured with fine wire had a greater tensile strength than that of similar wounds sutured with catgut or silk. In view of these encouraging reports we were led to investigate further the behavior of fine alloy steel wire when employed as a suture material in both animal and human tissues and to attempt to estimate its relative merits in comparison with the more commonly used materials.

EXPERIMENTAL STUDY

Four groups of experiments were conducted in order to compare the tissue reaction produced by alloy steel wire sutures with that produced by silk or catgut sutures in both aseptic and infected wounds. The wire employed in all of the experiments was size 35. It is a whitish pliable hair-like string having a diameter of 0.0007 of an inch and a tensile strength of 2.5 pounds (1).

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Group 1. Tissue Reaction in Aseptic Wounds

Procedure. Incisions 5 centimeters in length were made in the abdominal wall of dogs deeply enough to expose the anterior sheath of the rectus muscle. Three interrupted sutures of the alloy steel wire were applied through the rectus sheath and a part of the muscle in each wound. Three similar sutures of either silk or catgut were applied in the same wound for the purpose of comparison and control. All of the sutures were applied with fine curved needles of the same size. The wounds were reopened at different intervals after the operation and gross changes around the sutures were noted. This was followed by the excision of blocks of fascia and muscle bearing the sutures, for the purpose of microscopical study. The specimens were fixed in a 10 per cent solution of formalin. The wire sutures were removed after the fixation and sections were made through the fascia and the muscle at the places through which the sutures had passed. All sections were stained with hematoxylin and eosin. The control sutures consisted of silk, both No. C (medium silk) and No. A (fine silk) grades; plain catgut, No. 1 and No. 00; and chromic catgut, No. 1 and No. 00. Observations were made at periods varying from 24 hours to 20 days after original application of sutures. Altogether 21 wounds were studied.

Gross examination. Wire sutures. In recent wounds, no inflammatory reaction was observed in the tissues around the sutures. However, most of the sutures appeared tighter than at the time of the original application, causing a slight constriction of the fascia. In the wounds more than 1 week old, the wire was covered by a thin layer of fibrous tissue. Staining or necrosis of tissues around sutures was not noticed and the color and luster of the wire remained practically unchanged.

Silk sutures. Slight to moderate edema and necrosis were observed in wounds 2 and 5 days

old. Although of less intensity than those observed around the catgut sutures, these changes, in contrast to those around the wires, were very distinct. After 9 days, the sutures were found to be buried in a rather heavy layer of fibrous tissue. In a few specimens, a small amount of cloudy fluid was found around the sutures as long as 20 days after they had been applied.

Catgut sutures. Moderate edema, slight necrosis, and a small amount of turbid exudate were invariably observed around the catgut sutures in wounds less than 5 days old. The reaction around the plain catgut was especially marked. That around the No. 00 sutures was slightly less than that around the No. 1 sutures of both plain and chromic gut. Plain catgut began to show evidence of disintegration on the fourth or fifth day and usually had totally disappeared after 7 days. The chromic catgut sutures were fairly well preserved for the first 2 weeks; after 20 days they were found to have disappeared.

Microscopic examination. Wire sutures. Sections of tissue from 24 hour to 3 day old wounds showed the presence around each suture of a thin layer of hyalinized material probably formed as a result of compression of the tissues by the sutures. In the surrounding tissue, there was slight leucocytic infiltration, some edema, and occasionally a small amount of fibrinous exudate. In the 4 day wound there was slight proliferation of fibroblasts and infiltration with lymphocytes and plasma cells in the neighborhood of the sutures. In the wounds more than 7 days old, the number of fibroblasts decreased while the amount of intercellular collagen fibrils increased. Granulation tissue was not observed. Aside from some atrophy of the muscle fibers in immediate neighborhood, there was no other evidence of damage to tissues.

Silk sutures. The tissue reaction to the No. A silk was less than that to the No. C silk sutures. However, the difference was not marked, and they are described together. In wounds less than 5 days old the sutures were surrounded by some necrotic tissue infiltrated by a large number of leucocytes. In the non-necrotic tissue in the neighborhood there was moderate leucocytic, and occasionally also fibrinous, exudate. After 5 days the acute inflammatory reaction began to subside. However, among the filaments of the sutures there usually were some leucocytes. At the same time there was fibroblastic proliferation and infiltration of lymphocytes, plasma cells, and large mononuclear phagocytes. The latter often were crowded together in close apposition to the sutures; later foreign body giant cells frequently were seen. In tissues from wounds 13 to 20 days old, the acute inflammatory reaction usually had largely disappeared, but a few leucocytes remained among filaments of the sutures or in their immediate neighborhood. The sutures were surrounded by a broad zone of newly formed fibrous tissue.

Catgut sutures. The plain and the chromic sutures of the same size caused a very similar reaction, but the finer sutures (No. 00) produced relatively less reaction than the heavier ones (No. 1). A description of the microscopic findings of the tissues sutured by No. 1 chromic catgut will suffice. A very intense and extensive acute inflammatory reaction was observed around the sutures in wounds from 1 to 5 days old. The reaction was not limited to the immediate neighborhood of the sutures but involved the adjacent tissues for some distance. There was heavy leucocytic infiltration, marked fibrinous exudation, congestion, and edema. The leucocytic infiltration was so intense around the sutures that small abscesses were often formed. The tissues surrounding the sutures, including the muscles, usually showed necrosis. In the 4 day specimens, granulation tissue began to appear and reached the maximum amount on the seventh to the ninth day. The sutures at this time still were surrounded by a zone of leucocytic exudate. The granulation tissue was infiltrated by many leucocytes, lymphocytes, plasma cells, and numerous large phagocytes containing many nuclear fragments and fatty droplets. There was no tendency for these phagocytes to form foreign body giant cells. In the specimens from wounds more than 9 to 13 days old, there was considerable fibrosis in the granulation tissue, but marked leucocytic infiltration still was observed in the immediate neighborhood of the partially absorbed catgut sutures. The majority of the sutures began to show fragmentation and penetration by leucocytes as early as the fourth or fifth day. A few appeared to be intact up to the thirteenth day.

Summary. Table I summarizes the tissue reaction around the different kinds of sutures as observed at varying intervals after they had been placed in position. It will be seen that the wire sutures caused very slight initial acute inflammatory reaction followed by a slight amount of fibrosis without the formation of actual granulation tissue. The silk sutures produced a more acute inflammatory reaction, some granulation tissue and much fibrosis. The catgut sutures caused a very severe acute inflammatory reaction in the early wounds with frequent formation of minute abscesses. This was followed by extensive granulation and fibrosis. These changes are illustrated in Figures 1 to 4.

TABLE I.—TISSUE REACTIONS TO FINE ALLOY STEEL WIRE, SILK, AND CATGUT SUTURES IN ASEPTIC WOUNDS OF DOGS

Reaction	Acute inflammatory reaction							Granulation tissue							Fibrosis						
Suture	Wire	Silk		Plain catgut		Chromic catgut		Wire	Silk		Plain catgut		Chromic catgut		Wire	Silk		Plain catgut		Chromic catgut	
Duration of wound —days	No. 35	No. C	No. A	No. 1	No. ∞	No. 1	No. ∞	No. 35	No. C	No. A	No. 1	No. ∞	No. 1	No. ∞	No. 35	No. C	No. A	No. 1	No. ∞	No. 1	No. ∞
1	+				+++ ++		++ ++	−				−		−	−				−		−
2	±	+++	++			+++ ++		−	−	−			−		−	−	−			−	
3	±			++ ++				−			−				+			−			
4	±				+++		+++ ++	−				+		+	++				−		−
5	±	+	+	+++ ++		++ ++		−	+++	++	−		++ ++		++	+	+	−		+	
7	−			++ ++	++		+++	−			++ ++	++		+++	+			−	+++		+
9	−	±	±			+++		−	++	++			++ ++		+	+++	++			++	
13	−	−				++		−	±				+++		+	++				+++	
20	−	−						−	±						+	++					

Group II. Tissue Reaction in Infected Wounds

Procedure. The procedure employed was essentially similar to that in Group I, except that the sheath and fibers of the rectus muscle were divided down to the peritoneum and 1 cubic centimeter of a 24 hour broth culture of Bacillus coli was introduced into the wound before the sutures were applied. Wire sutures were employed to reapproximate the rectus sheath throughout one half of the incision; for controls No. C silk was used to close the other half of the rectus sheath in 4 wounds and in another 4 wounds No. 1 chromic catgut was employed. Observations were made, and tissues were removed for microscopic examinations on the 2nd, 5th, 8th, and 14th days after the application of the sutures.

Gross examination. All wounds became swollen after 48 hours and showed signs of mild suppuration during the next few days. By the end of one week, most of the wounds appeared to have healed externally. At the time of removal of the specimens, however, from 2 to 3 cubic centimeters of pus was evacuated from each of the 2 and 5 day wounds and from the 8 day wound containing catgut. In 3 other wounds, 1 of 8 days containing silk and the 2 others of 14 days containing silk and catgut, respectively, there was no free fluid. There was surprisingly little reaction around the wire sutures in any of the wounds even when free pus was present. Around the catgut, extensive necrosis and fibrinous exudate were noticed. In the 14 day specimen, the sutures were partially dissolved and came out on slight manipulation. However, in the 8 day specimen, most of the catgut sutures still were intact although surrounded by purulent exudate. An intermediate reaction was seen around the silk sutures. In the 8 and 14 day specimens the wounds were healed and clean. Immediately around the silk, a small amount of mucogelatinous exudate remained.

Microscopic examination. Wire sutures. The sutures in the 2 day old wound were surrounded by a small amount of leucocytic and fibrinous exudate which was continuous with a similar exudate present throughout the wound. In the 5 day wound the acute reaction around the sutures had subsided and fibroblasts had appeared, although signs of acute inflammation still were present in the tissues farther removed from the sutures. In the 8 day specimen the sutures were surrounded by a thin layer of hyaline material. The acute inflammatory reaction in the surrounding tissues also had subsided and granulation tissue infiltrated by lymphocytes and plasma cells had appeared. In the 14 day wound, the sutures were surrounded by an inner thin layer of hyaline material and an outer fairly broad zone of fibrous tissue.

Silk sutures. In the 2 day wound, the sutures were infiltrated by leucocytes and surrounded by a moderate amount of serofibrinous and leucocytic exudate. In the 5 day wound, the acute inflammatory reaction in the surrounding tissues had become much more extensive. At 8 days,

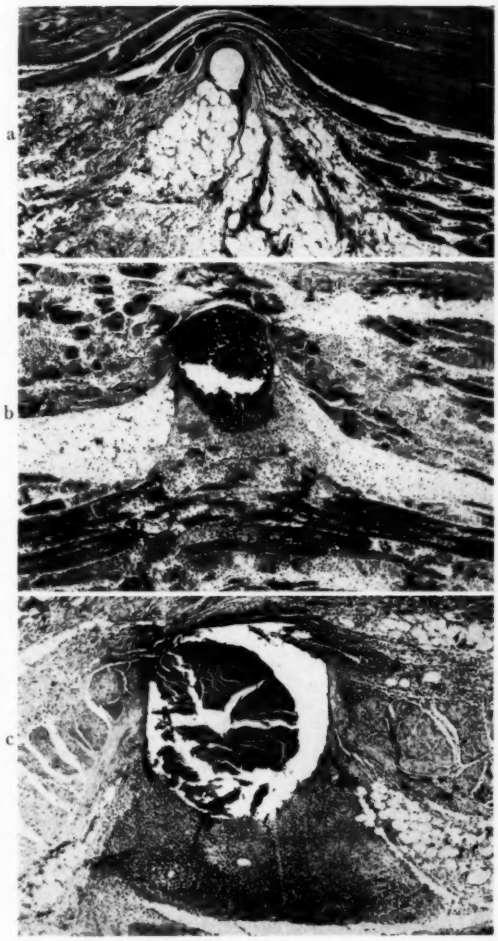


Fig. 1. Tissue reaction to sutures, 2 days after application. ×40. a, Wire (represented by an oval empty space in all illustrations): Note absence of cellular infiltration around suture and only slight inflammatory reaction in surrounding tissues. b, No. C silk: Suture is partially encircled by purulent exudate with moderate inflammatory reaction in surrounding tissues. c, No. 1 chromic catgut: Very extensive acute inflammatory cellular infiltration.

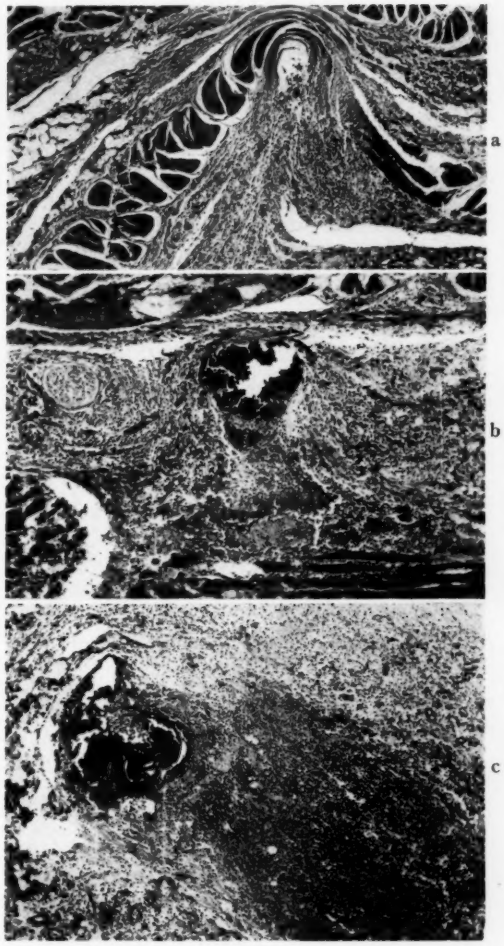


Fig. 2. Tissue reaction to sutures, 5 days after application. ×40. a, Wire: There are a moderate number of fibroblasts around the suture. Note the marked constriction on the tissue in this section. b, No. C silk: The acute inflammatory reaction in the surrounding tissues is subsiding; granulation tissue has formed in the surrounding tissues. c, No. 1 chromic catgut. Very extensive purulent exudate still is present.

the sutures were surrounded by granulation tissue which was infiltrated chiefly by leucocytes and to a less extent by lymphocytes, plasma cells, and large mononuclear phagocytic cells. In the 14 day specimen extensive granulation tissue had formed and there was very active proliferation of fibroblasts, especially around the sutures. Large numbers of leucocytes still were present; some of them were among the filaments of silk. A large number of mononuclear phagocytes were scattered among other cells in the granulation tissue, but they did not encroach upon the sutures.

Catgut sutures. Sutures in the 2 day wound were surrounded by a large amount of fibrinopurulent exudate which became even more abundant after 5 days. Fragmentation of the

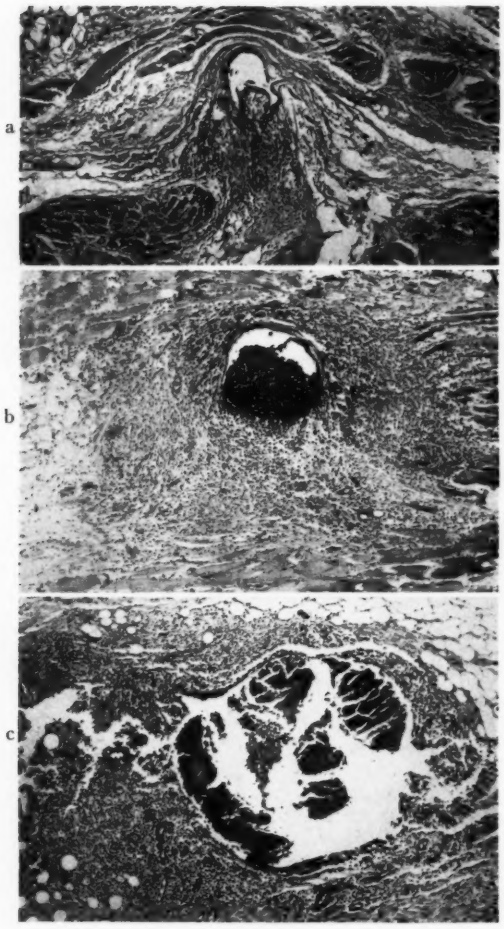


Fig. 3. Tissue reaction to sutures, 9 days after application. ×40. a, Wire: The inflammatory reaction has entirely subsided; slight fibrosis is seen. b, No. C silk: The suture is surrounded by organizing granulation tissue. c, No. 1 chromic catgut: Fragmentation of the suture has occurred. There still is much leucocytic infiltration and granulation tissues.

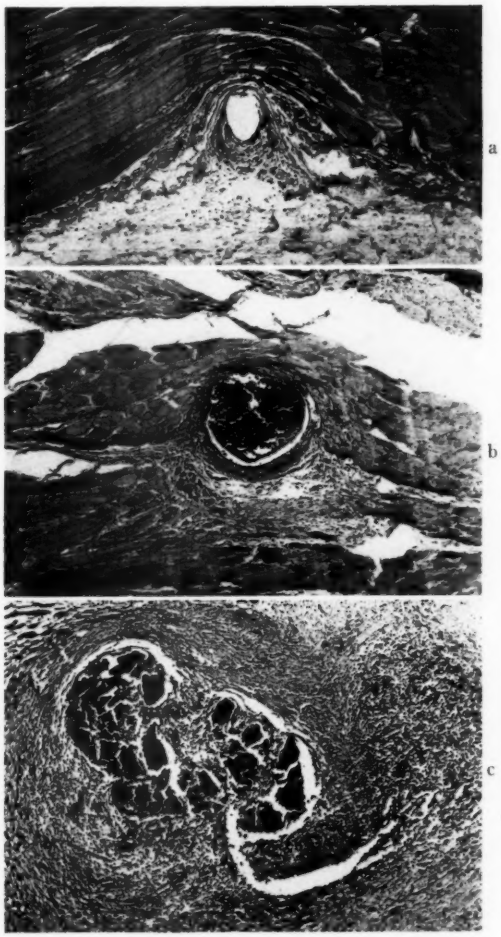


Fig. 4. Tissue reaction to sutures, thirteen days after application. ×40. a, Wire: Very little fibrosis is seen. b, No. C silk: Moderate fibrosis. c, No. 1 chromic catgut: The suture still is surrounded by granulation tissue. Fibrosis is taking place at the periphery. Note the infiltration of leucocytes between the fragments of the suture.

sutures with penetration of leucocytes was observed in the 5 day specimen. In the 8 day specimen, the sutures appeared as fragments in the center of an abscess lined by a wall of granulation tissue heavily infiltrated by leucocytes. Only a few lymphocytes, plasma cells, and large mononuclear phagocytic cells were present. By 14th day, picture still was the same, except that there was more fibrosis of the granulation tissue.

Summary. The tissue reaction to wire, silk, and catgut sutures in infected wounds is summarized in Table II. In the 2 and 5 day specimens, there was a diffuse inflammatory reaction throughout the whole wound as a result of the infection. However, the reaction in the immediate neighborhood of the sutures varied according to the suture material. The cellular infiltration around the wires was no heavier than that else-

TABLE II.—TISSUE REACTIONS TO FINE ALLOY STEEL WIRE, SILK, AND CATGUT SUTURES IN INFECTED WOUNDS OF DOGS

Duration of wounds—days / Reaction / Suture	Acute inflammatory reaction			Granulation tissue			Fibrosis		
	Wire	Silk	Catgut	Wire	Silk	Catgut	Wire	Silk	Catgut
2	+	+++	+++ ++	−	−	−	−	−	−
5	+	+++	+++ ++	−	−	−	+	−	−
8	−	++	++ ++	−	+++	++ ++	+	+	−
14	−	+	++ ++	−	+++	++ ++	+	++	−

where in the wound; the silk and catgut sutures, on the other hand, were surrounded by many more leucocytes. In the wounds of 8 and 14 days (Fig. 5 and 6), the difference was even more striking. The inflammatory reaction around the wire sutures had subsided, but the silk and catgut sutures still were bathed by purulent exudate.

Group III. Peritoneal Reaction

Procedure. Rectus incisions 4 inches in length were made on each side of the midline of the abdominal wall of 4 dogs. The peritoneum was incised along the entire length of each incision, but the structures within the peritoneal cavity were not disturbed. The peritoneum was reapproximated with a continuous suture of No. 1 chromic catgut in the upper half and a continuous suture of No. 35 alloy steel wire in the lower half of the incision on the right side. On the left, a continuous wire suture was employed in the upper half and a continuous suture of No. C silk in the lower half of the incision. The rectus sheath and the skin were closed with interrupted sutures of No. A silk on both sides. These animals were sacrificed 7, 11, 14, and 21 days later, respectively.

Results. In the first 3 dogs, identical pictures were observed. In the areas sutured with catgut or silk, the whole line of the peritoneal incision was covered by adherent omentum while the portions sutured with wire were entirely free and were represented by linear scars (Fig. 7). In the fourth dog, the segment sutured with silk was covered heavily by omentum while the other three areas all had healed without adhesions.

Group IV. Healing of Infected Wounds

Procedure. The method used in this series of experiments was similar to that employed by Shambaugh and Dunphy (13) in their study of the relative merits of silk and catgut sutures in infected wounds, except that fine alloy steel wire was used with silk and catgut for controls.

A rectus incision down to but not through the peritoneum was made on each side of the midline of the abdominal wall of a dog. To each of the wounds, 1 cubic centimeter of a saline suspension of dog's feces was applied in order to produce marked infection. On the right side the rectus sheath was closed by means of interrupted sutures of No. 35 alloy steel wire. The same material was used for ligating bleeding points in the wound. On the left side an equal number of interrupted sutures of No. 1 chromic catgut was employed. No. 1 plain catgut was used for ligating bleeders. The skin was closed with interrupted sutures of fine silk on both sides. This procedure was carried out in 2 dogs. In another 2 dogs, a similar procedure was employed except that in the left rectus wound, No. C silk was used for the anterior rectus sheath and No. A silk for ligating bleeding vessels. All the wounds were examined daily. Alternate skin stitches were removed 3 days, and the remaining stitches 5 days, after the operation. When an accumulation of pus was noticed, the wound margins were separated with a clamp and gentle pressure was applied to the rest of the wound in order to evacuate the discharge. No other treatment was given except the application of a sterile dry dressing after each examination.

Results. All wounds were swollen and frankly suppurating 48 hours after the operation. The initial swelling was most marked in those wounds closed with catgut, least in those closed with wire, and intermediate in those in which silk had been employed. The amount of pus evacuated on the first separation of the wound corresponded closely to the degree of the swelling. The wounds closed with wire progressed rapidly toward healing as soon as the pus was evacuated. By the end of the first week, all discharge had ceased. All four wounds sutured with wire healed completely by the end of 2 weeks. None of the wire sutures was discharged. The two wounds closed with catgut showed the largest amount of discharge.

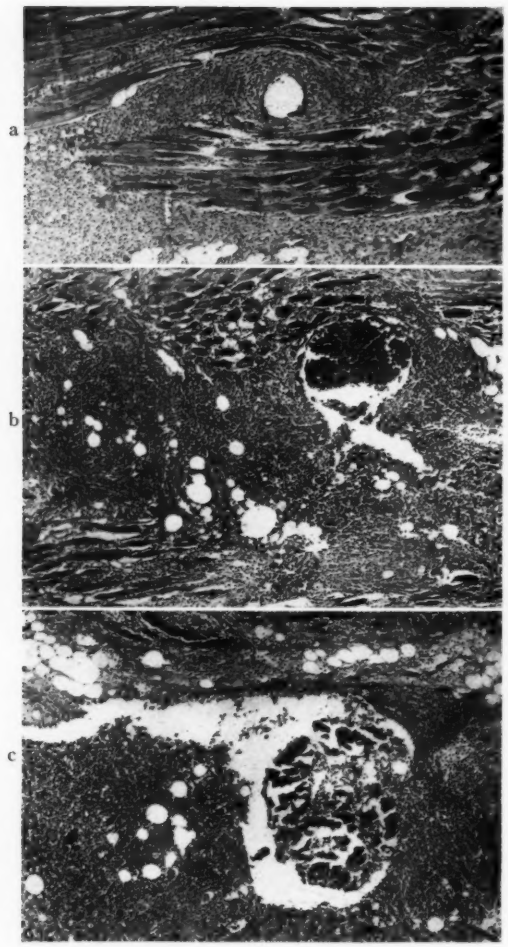


Fig. 5. Tissue reaction to sutures in infected wounds, 8 days after application. ×40. a, Wire: The inflammatory reaction has subsided and fibrosis has begun. b, No. C silk: Extensive granulation tissue formation is evident with infiltration of leucocytes around and into the suture. c, No. 1 chromic catgut: The reaction is even more marked than in b; note marked fragmentation of suture.

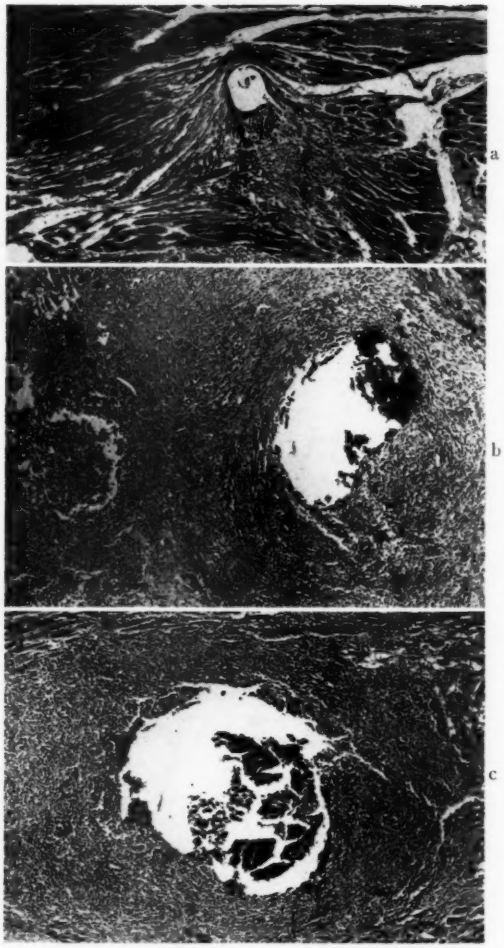


Fig. 6. Tissue reaction to sutures in infected wounds, fourteen days after application. ×40. a, Wire: Slight fibrosis. b, No. C silk: The suture is surrounded by granulation tissue with marked leucocytic infiltration. c, No. 1 chromic catgut: The suture has been partially absorbed. Extensive granulation tissue and purulent exudate are present.

More than half of the sutures escaped with the pus on the fourth and fifth days. These wounds healed 8 and 10 days, respectively, later than those closed with wire (Fig. 8). During the first 2 weeks, the wounds closed with silk progressed better than those closed with catgut, although they showed more swelling and discharge than those in the same animals closed with wire. However, they drained for a longer period of time. After 2 weeks, while the wounds closed with wire in the same dogs had healed completely, a discharging sinus persisted in each of the wounds closed with silk (Fig. 9). In one dog, the sinus closed spontaneously 16 days later; in the other, it persisted for 43 days without sign of healing. When the sinus tract was laid open, it was found to

be lined by soft gelatinous granulation tissue within which were buried five silk sutures. These were removed, and the wound healed 10 days later.

CLINICAL STUDY

During the past year, one of us (Y. K. W.) has used fine alloy steel wire as the main suture material for the closure of 40 abdominal incisions. In each instance the peritoneum was closed with a continuous suture of No. 1 chromic catgut, the anterior rectus sheath was reapproximated with figure-of-eight sutures of No. 35 alloy steel wire, the subcutaneous layer was closed with interrupted sutures of the same material (in thin individuals this layer of sutures was omitted), and the skin was brought together with interrupted sutures of No. A silk. Hemostasis was secured largely by electrocoagulation.

All of the incisions, with three exceptions, were of rectus or paramedian type, varying from 10 to 20 centimeters in length. More than two-thirds of the operations involved the opening of the lumen of the gastrointestinal tract. There were 14 gastrostomies, 1 total and 2 partial gastrectomies, 7 instances of resection and anastomosis of the small or large intestine, 6 operations for intestinal obstruction (enterostomy, colostomy, division of peritoneal adhesions, etc.), 2 instances of simple exploratory celiotomy, and 8 other operations upon the spleen, liver, and biliary tract. Thirty-seven of the 40 wounds were clinically aseptic while 3 were made through contaminated fields. These two groups are considered separately.

Group I. Clean Wounds

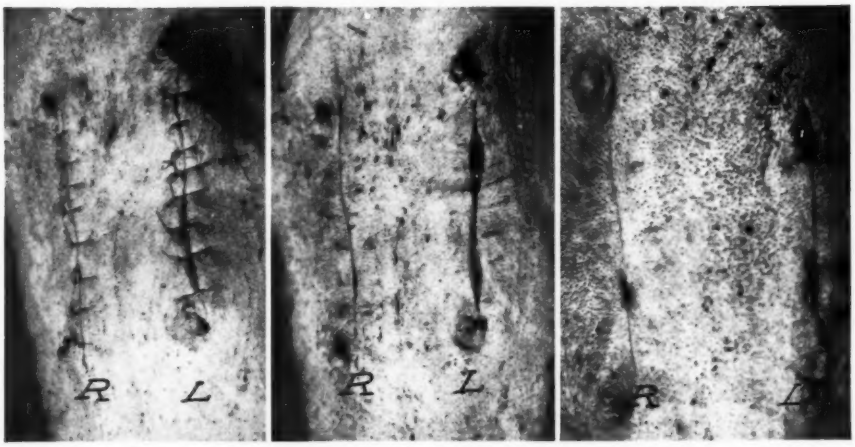
Two patients of this group did not recover from the operation. However, at the time of death, 1 and 5 days, respectively, after the operation, the wounds showed no sign of infection. The wounds in the other 35 patients healed *per primam*. It was our general impression that the induration along the line of the incision during the course of healing of these wounds was definitely less than that in wounds closed with either catgut or silk. No patient had undue pain or other complaint that could be attributed to the presence of the wires. Even in thin individuals, when the sutures could be palpated through the skin, there was no tenderness. In no instance did a suture work out through the skin during the period (a few weeks to a few months) this group of patients was under observation. Four patients with carcinoma of the esophagus died in the hospital from 1 to 8 months after gastrostomy. Postmortem examination showed that all the wire sutures were well preserved and without evidence of gross change.

Fig. 7. Peritoneal surface of abdominal wall of dog showing parallel rectus incisions closed with continuous sutures of different material: *A* and *D*, No. 35 alloy steel wire; *B*, No. C silk; *C*, No. 1 chromic catgut. Specimen excised 2 weeks after operation. Note the smooth healing in the sections sutured with wire and the heavy omental adhesions in the sections sutured with catgut or silk.

Microscopic examination of the tissues around the sutures revealed a minimal amount of fibrosis.

The largest group in this series of cases was that of gastrostomy of the Janeway type for patients suffering from carcinoma of the esophagus. It was with the idea of reducing an excessively high incidence of postoperative wound infection in this group of debilitated patients that we first began to employ wire sutures for the closure of the abdominal wound. During the last 4 years, 62 operations of this nature have been performed by 8 surgeons in the Peiping Union Medical College Hospital. The incidence of infection and disruption of the wounds, grouped according to the suture material used for the closure of the abdominal wall, is shown in Table III.

It is not justifiable to draw any conclusion concerning the small group of cases in which catgut was used, although the fact that infection and disruption occurred in 2 of the 3 cases suggests that catgut is an unsuitable suture material. In comparing the incidence of complications in the 2 other groups, there was a marked lowering of the rate of infection in the group in which wire was used, but the incidence of disruption was



a b c

Fig. 8. Abdominal wounds infected with a saline suspension of dogs' feces. The rectus sheath has been closed with No. 35 alloy steel wire on the right side and No. 1 chromic catgut on the left side. a, 3 days after operation. Wire wound, slightly swollen. Less than 10 cubic centimeters of pus evacuated. Catgut wound, markedly swollen; 30 cubic centimeters of pus evacuated. b, 5 days after operation. Wire wound, healing; discharge scanty. Catgut wound, still swollen with moderate amount of pus. c, 12 days after operation. Wire wound, almost completely healed. Catgut wound, still discharging pus. Whole incision is undermined; complete healing, 10 days later.

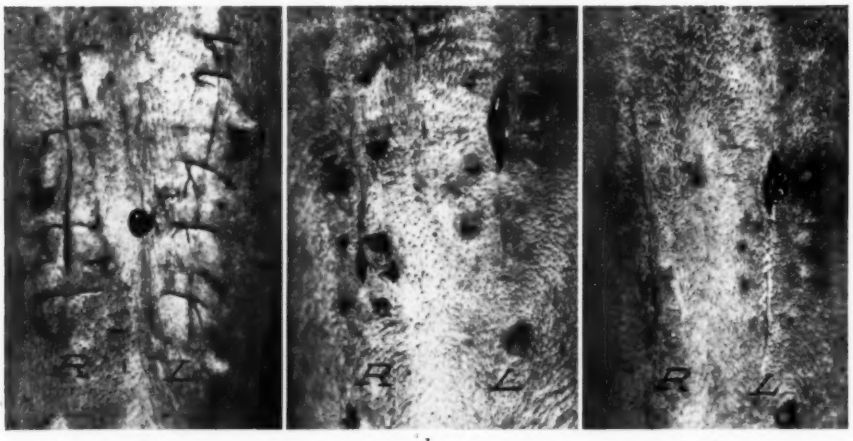


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Fig. 9. Abdominal wounds infected with a saline suspension of dogs' feces. The rectus sheath has been closed with No. 35 alloy steel wire on the right side and No. C silk on the left side. a, 3 days after operation. Wire wound, moderately swollen; 5 cubic centimeters of pus evacuated. Silk wound, markedly swollen; 10 cubic centimeters of pus evacuated. b, 7 days after operation. Wire wound, healing, except for superficial necrosis; discharge scanty. Silk wound, moderately swollen with purulent discharge. c, 14 days after operation. Wire wound, completely healed. Silk wound, upper two-thirds of wound undermined. Wound drained for 43 days and healed only after it was reopened and some silk sutures removed.

distinctly higher in this group than in the group in which the wound was closed with silk. However, in the 2 instances in which disruption of the wound occurred following closure by wire, the patients suffered from severe attacks of coughing. One developed bronchopneumonia after opera-

TABLE III.—COMPLICATIONS OF ABDOMINAL INCISIONS IN JANEWAY GASTROSTOMIES FOR CARCINOMA OF THE ESOPHAGUS

Type of suture material	Cases	Infection		Disruption	
		Number	Percentage	Number	Percentage
Catgut	3	2	66.7±22.5	2	66.7±22.5
Silk	36	9	25.0±4.9	1	2.8±1.9
Wire	23	2	8.7±4.1	2	8.7±4.1
Whole series	62	13	21.0±3.5	5	8.1±2.3

tion. His wound became infected due to necrosis of the gastrostomy stump and ruptured on the seventh postoperative day. The other patient developed a tracheoesophageal fistula at the site of the carcinoma. Violent attacks of coughing followed and the wound broke open on the eighth postoperative day.

Since factors other than the type of suture material employed must be considered in the problem of the healing of wounds, it may be worthwhile to compare the incidence of complications following the same type of operation performed by the same operator. The personal series of Janeway gastrostomies for carcinoma of the esophagus of one of us (Y. K. W.) consists of 22 operations. One of 2 wounds closed by catgut became infected and disruption followed; 2 of 7 wounds closed by silk became infected, with disruption in 1; but all of 13 wounds closed by wire healed without complication.

Group II. Contaminated Wounds

In 3 of the 40 cases in this series, the wounds were contaminated grossly at the time of operation.

CASE 1. In an infant 6 months of age, excision of a congenital umbilical fistula due to a patent omphalomesenteric duct was carried out. The incision was made through the macerated skin around the umbilicus. The wound was closed with wire sutures and healed without sign of infection.

CASE 2. In performing a splenectomy for cirrhosis of the liver, it became necessary to extend the incision through an infected area of the abdominal wall. On the sixth day, a localized abscess was found beneath the skin at the site of the original infection. Following separation of the edges of the wound in this area the infection subsided promptly. Complete healing occurred within 2 weeks.

CASE 3. During an operation for the repair of a fecal fistula, the wound was contaminated by the unexpected opening of a peritoneal abscess. The main portion of the wound was closed with wire sutures, but the end overlying the abscess was left open for drainage. In spite of the poor general condition and marked nutritional disturbance of the patient, the sutured portion of the wound healed promptly and the whole wound closed by the 28th postoperative day. It was not necessary to remove any of the wire sutures during the healing of the wound, nor were any of these sutures extruded spontaneously.

Fig. 10. Diagram showing the correct, a, left, and incorrect, b, method of twisting the wire sutures.

In several other instances in this clinic contaminated wounds closed with fine alloy steel wire (by other surgeons) showed a similar favorable response. The wounds either healed without clinical evidence of infection or only mild infection developed. Even in the presence of frank suppuration, the wire sutures remained in position and became covered by healthy granulations within a relatively short period of time.

FIXATION OF WIRE SUTURES BY TWISTING

The chief objection to the use of alloy steel wire sutures is the difficulty of handling and tying the wire. In order to simplify this procedure, we merely twisted the ends of the wire three complete turns instead of attempting to form the usual type of knot. Sometimes the twisted ends (which were 2 to 3 mm. in length) were turned downward with a hemostat. By this method, we not only could anchor the individual sutures in a much shorter period of time, but also could regulate the tension of the sutures more accurately than by the classical formation of knots. The last mentioned point constitutes an important reason for the use of this method of fixation of the wire sutures. It is imperative, however, that the two ends of the wire be twisted equally so that they will lock and maintain their position (Fig. 10).

This method of fixing the wire sutures was used in most of the experimental animals. None of the sutures was found to have become untwisted or to have shifted from its original site at the time at which the specimen was removed. The method also was employed in 10 patients. All wounds healed without complication. In 7 instances in which subsequent roentgenological examination was carried out, the wire sutures were found to be in satisfactory position.

EVALUATION OF STUDY

We believe that this study has demonstrated a less severe reaction of the body tissues to fine alloy steel wire sutures than to either catgut or silk, under both septic and aseptic conditions. The evidence presented by the illustrations alone (Figs. 1 to 9) is so striking that further comment scarcely seems to be necessary. However, we may summarize our observations in the following manner: Fine alloy steel wire sutures initiate only a very mild inflammatory reaction in the surrounding tissues. Even this reaction

seems more likely to be due to trauma incidental to the passage of the needle and the suture than to the continued presence of the wire. This reaction soon subsides and is replaced by the healing process. In the instance of silk, the initial reaction is distinctly more marked and the subsequent fibrosis also is relatively more extensive. In infected wounds leucocytes and granulation tissue not only appear around the sutures but also infiltrate between the filaments of the silk. Therefore, until the sutures are removed the infection is likely to persist. As Meade, Jackson and Ochsner have pointed out, this is the chief reason why the presence of silk sutures may seriously delay the healing of infected wounds. Catgut sutures produce the most extensive early as well as delayed type of inflammatory reaction. As a matter of fact, a majority of all catgut sutures actually lie bathed in minute aseptic abscesses until their filaments are largely or completely absorbed. These changes certainly predispose toward infection of the wound. Furthermore, in the presence of infection, catgut sutures either are dissolved or sloughed off before solid healing of the wound has had time to occur. This leads to disruption of the wound in certain instances.

From these observations, it may be suggested that catgut is not a suitable suture material for the closure of either aseptic or infected wounds. Silk is a generally satisfactory material for clean wounds, but is to be avoided in the presence of infection. Fine alloy steel wire is preferable to either catgut or silk for both clean and infected wounds. We believe this type of wire to be especially suitable for the closure of abdominal wounds after operations in which there is a potential chance of contamination, as in extensive resections or anastomoses of gastrointestinal tract. In presence of frank infection, fine alloy steel wire is undoubtedly the suture material of choice.

In using wire sutures, the general principles laid down by Halsted for the use of silk should be rigidly observed, with special emphasis on the avoidance of tension. In our experience, No. 35 alloy steel wire is satisfactory for suturing both the aponeurosis and the subcutaneous fascia. Thicker and stronger wire is probably unnecessary. The wire can be sterilized by boiling or autoclaving. It may be sterilized repeatedly without loss of strength. The low cost of the wire (2) is another distinct advantage.

SUMMARY AND CONCLUSIONS

1. The behavior of fine alloy steel wire sutures was studied in dogs, catgut and silk sutures being used as controls. Gross and microscopic observations were made in both aseptic and infected wounds. It was found that wire sutures produced the least amount of tissue reaction and promoted the most rapid healing of the wounds.

2. Clinical experience with forty abdominal incisions closed by fine alloy steel wire sutures showed that all clean wounds healed *per primam*. Reduction in the incidence of wound infection was especially remarkable in a group of Janeway gastrostomies established for patients suffering from carcinoma of the esophagus. In 3 instances of contaminated wounds, primary healing occurred in 1 and only localized infection developed in the 2 others, both of which healed without disruption and without extrusion of the suture material.

3. On the basis of these observations, more extensive use of fine alloy steel wire sutures is recommended, especially in wounds potentially or obviously contaminated. We realize, however, that the final evaluation of this type of suture can be determined only by careful observation of the immediate as well as the late results in a much larger number of cases.

4. In using wire sutures, the rules laid down by Halsted for the use of silk should be followed closely. Special emphasis should be placed on the avoidance of tension when the sutures are tied. The fine caliber and the unyielding character of the wire tend to cause it to constrict and to cut through the tissues if this precaution is not observed.

5. In order to facilitate the tying of wire sutures and the regulation of the tension exerted by them on the tissues within their grasp, we recommend elimination of the customary knot and fixation of these sutures by simple twisting of the ends of the wire for three complete turns.

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PERITONEAL ASPIRATION IN THE DIAGNOSIS OF STRANGULATED BOWEL

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DURING the course of some experiments on dogs in which a loop of strangulated bowel was placed in a rubber bag, we observed that within a few hours the bag began to fill with an exudate, profuse in amount, which had a cherry-red or pink color. This fluid appeared before the loop ruptured and the redness of its color gradually increased until after the loop ruptured, when it of course, took on the appearance of the contents of strangulated bowel. We showed in the previous investigations (3) that this fluid is toxic when injected intravenously into another animal. In order to confirm the presence of this exudate, in the absence of the rubber bag although it has been previously mentioned by Scott and Wangensteen who studied the fluid found in various types of obstructions in dogs, we produced strangulated loops of bowel 4 inches long in another series of dogs. We found that fluid which was exactly similar to the fluid present in the bag formed in the abdominal cavity in these animals. The fluid contains blood, and the erythrocytes are present in approximately the concentration which is produced when one drop of blood is placed in one cubic centimeter of water.

Richardson in 1920 called attention to this rusty, blood-stained fluid in cases of strangulation of the bowel and suggested that the appearance of such peritoneal fluid might aid in the diagnosis of intestinal obstruction after the abdomen had been opened. In a series of 135 cases of intestinal obstruction he found 21 in which there were strangulation of the bowel and this typical fluid. There were also a few cases in which, although there was interference with the mesenteric circulation, it was definitely stated that there was no rusty fluid. Richardson believed that these cases came to operation before the fluid had time to form. In some cases of simple obstruction he noted that clear, straw-colored fluid may be present. Scott and Wangensteen in their studies on various types of obstructions in dogs found that when the mesenteric veins were ligated, 50 to 250 cubic centimeters of hemorrhagic fluid having low protein content and little if any odor, developed. In those dogs with arterial or with both venous and arterial obstruction, 100 to 500 cubic centimeters of dark bloody foul-smelling fluid with high protein content was present.

Because of the striking character of this fluid and its positively diagnostic nature when present, we were led to perform a series of experiments on dogs in which we attempted to aspirate fluid from the abdominal cavity at various intervals after a strangulation obstruction had been produced. The procedures followed were the same on all animals: Under intratracheal ether anesthesia, and with the usual sterile precautions, a midline incision was made, and a segment of jejunum 4 inches long and 1 foot below the ligament of Treitz was ligated with cotton tape. The vessels of the mesentery were included in the ligature but the tape was not pulled tightly enough to obstruct the arteries. The abdomen was then closed in layers by the usual method. The peritoneal cavity was aspirated, a lumbar puncture needle being used at 1, 2, 4, and 6 hour intervals after the operation.

As shown in the accompanying table, in 2 dogs fluid obtained 1 hour after operation contained in one instance many red blood cells and white blood cells, and in the other, white blood cells only. At 2 hours, in 3 of 4 animals, fluid was obtained which under the microscope showed many red blood cells and white blood cells. Culture of this fluid showed no growth in one, and short chain streptococci and gram negative short rods in another. At 4 hours, aspiration of the abdominal cavity of all 4 animals revealed typical reddish fluid which was diagnostic of strangulation, and culture from this time on was always positive for bacteria which we did not identify. At 6 hours, in all animals, the same type of fluid was obtained. The animals died during the night, and in all cases the loop was found at necropsy to be ruptured. Two additional dogs were operated on and obstructed loops 2 feet in length were produced. These dogs were sacrificed at 14 to 18 hours, and the loops of bowel were found not to be ruptured. In each case about 40 cubic centimeters of the typical fluid was found in the peri-

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FOUR-INCH STRANGULATED LOOPS

Dog no. Weight in lbs.	Hours after obstruction	Amount of aspirated fluid	Color of fluid	Smear of exudate	Culture of exudate	Autopsy findings
547 23	2	1 drop	Clear	Few RBC; many WBC	Negative	Loop ruptured and sour smelling purulent fluid present. Loop black. Omentum and intestines bound together with adhesions
	4	4 drops	Rusty	Many RBC; WBC and large fat globules	Aerobic: few short chain streptococci Slight acid Anaerobic: few gram negative short rods	
	6	2 c.cm.	Rusty	Same as above	Aerobic: acid, no gas; morphology as above Anaerobic: pellicle forming gram negative short rods and short chain streptococci	
553 11	2	None				Loop ruptured and sour smelling fluid present. No adhesions
	4	1 drop	Rusty	WBC		
	6	3 drops	Rusty	RBC and WBC	Aerobic: acid, no gas Anaerobic: pellicle formed	
555 10	1	1 drop	Clear	WBC		Ruptured loop, sour purulent fluid, 100 c.cm.
	2	1 drop	Rusty	WBC many RBC		
	4	1 drop	Rusty	WBC and RBC	Aerobic: gram positive and gram negative short rods, many short chain streptococci, acid forming	
	6	5 drops	Rusty	WBC with few intracellular bacteria and many RBC	Anaerobic: pellicle and coalgas odor, gram negative, short rods	
560 12	1	1 drop	Clear	Many RBC and WBC		Ruptured loop same as above
	2	10 drops	Rusty	Many RBC and WBC	Aerobic: short chain streptococci Anaerobic: gram negative short rods	
	4	2 drops	Rusty	WBC—90% polymorphonuclears RBC	Aerobic: staphylococci, streptococci, gram negative, rods Anaerobic: short chain streptococci, gram positive, rods	
	6	8 drops	Rusty	Same as above	Aerobic: acid-forming short gram negative rods, short chain streptococci Anaerobic: same as above	

toneal cavity. Samples of this fluid were removed for culture and smear, and the findings agreed with those of the fourth and sixth hour punctures, but the quantity of organisms and cellular matter was much greater. In no instance, as far as we were able to determine, was the bowel punctured by the aspirating needle. As control experiments, a simple obstruction was produced by a tape in 2 other dogs and 18 hours later, no fluid was found on opening the peritoneal cavity.

Denzer (1, 2), and Neuhof and Cohen have previously reported on the value of peritoneal aspiration in the clinical diagnosis of various types of peritonitis, and all emphasize the safety of the procedure and point out the difficulty of puncturing the intestine. The bowel moves away from the point of the needle and it takes considerable force to enter into its lumen. If the bowel should happen to be adherent to the peritoneal wall at the site of the puncture, the intestine probably would be penetrated, but under these conditions the puncture would be of little importance since there would be no leakage into the peritoneal cavity. The site chosen for puncture is probably of little importance. If a mass is present it should be avoided and the needle, of course, should be inserted high enough above the symphysis to miss the bladder. We have performed aspiration on one patient with acute intestinal obstruction and considerable distention, and no puncture of the intestine occurred. It is not difficult to tell when the needle enters the peritoneal cavity, and with ordinary care we believe that the procedure is safe. It sometimes requires aspiration for as long as a minute to obtain the fluid, according to Denzer, and if no leakage of air into the peritoneal cavity is permitted before suction is applied, it is easier to aspirate the fluid. We are not reviewing the value of this procedure in the diagnosis of other intra-abdominal conditions, because Horsley and the authors previously quoted have already done so.

CONCLUSION

In the experimental animal, strangulated bowel can be diagnosed within 4 hours after onset by the aspiration of characteristic fluid from the abdominal cavity.

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EDEMA OF THE PANCREAS

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EDEMA of the pancreas has been described first by Archibald, and several years later as a clinical entity, by Zoepffel. The cause and nature of the edema is still obscure. Some authors believe it is not related to pancreatitis but is a disease by itself, due to inflammation or to retention of the pancreatic secretion in the ducts. Other authors consider it to be the precursor or a mild manifestation of pancreatitis or pancreatic necrosis. The appearance of an edematous pancreas gives the impression that one is not dealing with an edema as seen in inflammation or congestion of other organs. This is probably the reason why this process has not been called simply edema of the pancreas, but usually is called "glassy edema of the pancreas." Cutting into such an edematous organ reveals that the edematous appearance is due to a gelatinous imbibition of the tissues, which do not contain much free fluid; no free fluid is oozing from the cut surface of the edematous pancreas as seen in edema of other organs. A small quantity of free fluid accumulates, however, under the capsule and in the interlobular spaces of the pancreas, which can be aspirated for chemical determinations. In cases of edema of the pancreas in dogs as well as in humans just as in cases of acute pancreatitis, exudate is found in the peritoneal cavity containing a high concentration of pancreatic enzymes (2). These enzymes are undoubtedly derived from the pancreas. In animal experiments direct observation of the initial stages of pancreatic edema shows the exudation of fluid from the surface of the gland. These findings suggest that in edema of the pancreas (as in pancreatitis) a diffusion of pancreatic juice occurs first into the pancreatic parenchyma and later into the peritoneal cavity. In recently published animal experiments it has been shown that this subcapsular and interstitial edema fluid contains large amounts of pancreatic enzymes (2). It was concluded from this finding that edema of the pancreas is due to an imbibition of the pancreatic and peripancreatic tissues with pancreatic juice.

From the Department of Gastro-Intestinal Research, Michael Reese Hospital, Chicago. Aided by the A. B. Kuppenheimer Fund. A preliminary report read at the meeting of the American Physiological Society, April, 1941.

It is well known that ligature of the main or of all of the pancreatic ducts in dogs usually is not followed by edema of the pancreas. Injection of bile, duodenal juice, or other substances into one pancreatic duct followed by ligature of the duct, however, leads regularly to an edema of the organ within a few minutes. In order to find out whether edema of the pancreas could be produced by more or less physiological means, that is, by stimulating the gland while one or more ducts were obstructed, the following experiments were performed.

In 4 dogs, the main pancreatic duct and, in 2 dogs, the main and one accessory duct were ligated. The pancreas was observed 5 to 60 minutes after this procedure, and no edema was observed. At that time 3 to 4 milligrams per kilogram of body weight of secretin were injected intravenously, and within a few minutes (3 to 5) edema of the pancreas began to appear, spreading rapidly over the entire organ. Fifteen to 30 minutes later the entire pancreas had been involved extensively. The edema subsisted for a number of hours; then it subsided gradually and had disappeared almost completely 4 hours after injection. At that time a few fat necroses could be observed in the peripancreatic tissue of a few dogs. Some subcapsular edema fluid was aspirated at the height of the edema and was found to contain large amounts of amylase and lipase, similar to edema fluid obtained following injection of bile into the pancreas (2).

Peritoneal exudate was usually found as early as 15 minutes after administration of the secretin and likewise showed a high concentration of amylase and lipase. The increase of blood enzymes which is regularly observed after ligation of pancreatic ducts occurred much later than the finding of enzyme containing fluid in the peritoneal cavity.

In a control experiment the pancreatic duct was not ligated and secretin was injected intravenously. No change in the pancreas occurred within 1 hour, when the main pancreatic duct was ligated and the same amount of secretin was injected as before. A few minutes later an extensive edema of the pancreas developed.

In 4 dogs the main pancreatic duct was ligated and drugs which are known to stimulate pancreatic secretion, like mecholyl and eserine or pilocarpine were injected. This procedure was not followed by edema of the pancreas. In 1 dog .05 cubic centimeter of its own duodenal juice was injected into the main pancreatic duct, which was then ligated. Ten minutes later no change was noted. After that pilocarpine was injected subcutaneously and a few minutes later extensive edema of the pancreas developed.

Finally, in 1 dog both pancreatic ducts were ligated and one-tenth normal hydrochloric acid solution was infused into the duodenum at the rate of 40 drops per minute. Fifteen minutes after the beginning of the infusion of hydrochloric acid into the duodenum a marked edema of the pancreas developed in the central portion of the organ. The edema was not as extensive, however, as the one observed following injection of secretin. It is apparent that in this experiment the edema of the pancreas was produced by secretin liberated by the hydrochloric acid from the mucous membrane of the small intestine.

These experiments demonstrate that in the presence of complete or partial obstruction to the outflow of pancreatic juice an edema of the pancreas may be produced in dogs by injection of secretin or by the physiological mechanism of liberation of secretin in the small intestines, after acid gastric juice has entered the latter. The secretory effect of secretin is much greater than that of the vagotropic drugs applied, namely pilocarpine and mecholyl and eserine. It is possible that the production of edema of the pancreas in case of retention of secretion is dependent on the amount of secretion retained, in other words, on the degree of pressure developed within the ducts. However, the different composition of pancreatic juice secreted to secretin and to vagotropic drugs must be considered also. The experiment in which injection of a very small amount of duodenal juice into a pancreatic duct was not followed by edema but in which, following injection of pilocarpine edema developed points to an activation and potentiation of pancreatic enzymes within the duct system of the pancreas.

Our observations on dogs may be applied to man. It is a well known clinical observation that attacks of pancreatitis usually begin after a copious meal. If in such a person the outflow of pancreatic juice would be obstructed more or less completely, even for a very short period of time, the secretin mechanism activated by the hydrochloric acid from the stomach as well as by products of digestion would be sufficient to produce an acute edema of the pancreas.

SUMMARY

Pancreatic edema is produced by the diffusion of pancreatic juice into the pancreatic parenchyma and peripancreatic tissues. Extensive edema of the pancreas could be produced in animal experiments by ligation of a pancreatic duct and subsequent stimulation of pancreatic secretion by secretin, or by activation of the secretin mechanism by infusion of dilute hydrochloric acid into the duodenum. Under the same conditions stimulation of pancreatic secretion by vagotropic drugs did not lead to formation of edema.

These experiences may be applied to man in whom, under conditions of complete or incomplete obstruction of the pancreatic duct, the secretin mechanism activated by a meal may cause edema of the pancreas.

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JANUARY, 1942

CHANGING CONCEPTS OF THE ACCEPTED TREATMENT FOR ACUTE HEMATOGENOUS OSTEOMYELITIS

TEN years ago in most medical schools acute hematogenous osteomyelitis was considered an excellent example of acute infectious surgical disease. The necessity of making an extremely early diagnosis was emphasized; successful treatment was thought to be contingent entirely upon this. The treatment, almost the entire treatment, was then based upon drilling into the bone, the intention being to permit the escape of the infection. In 1920, the second edition of one popular textbook of surgery expressed this dominant idea, thus: "As soon as the diagnosis is made the bone should be opened. Delay even of a few hours is dangerous."

Acute hematogenous osteomyelitis is not a particularly common disease, a fact which may explain the now seemingly long delay in questioning whether the method of treatment being taught was the best form of management even for a decade ago. A real reckoning of the question revealed surprising figures. For example, in the Charity Hospital at New Orleans, from 1930 to 1936, inclusive, there were 112 primary cases of acute hematogenous osteomyelitis, that is, cases in which patients had not been operated upon elsewhere and not recurrent cases. In this group the accepted teaching that drilling the bone was the essential part of treatment was followed; in 84.8 per cent of the cases the initial operation involved opening the bone. Operation was performed in over 71.4 per cent of the cases within 48 hours after patients were admitted to the hospital and in 90 per cent of these the bone was opened. Thus in 64.3 per cent of all the cases the bone was opened within 48 hours after the patient entered the hospital. The surprising mortality for the entire series was 26.2 per cent, and for those operated upon within 48 hours after admission to the hospital, 32.2 per cent. Obviously something was wrong. This and many other analogous reports showed that operation was not accomplishing what surgical teaching maintained it would. From 1927 through 1940, 66 patients with primary acute hematogenous osteomyelitis have been admitted to Charity Hospital. In this group is reflected a much more conservative attitude regarding operation, for 36.4 per cent of the patients were operated upon during the first 48 hours after entrance to hospital but in only 27.3 per cent of the 66 patients was operation involving the opening into a bone done within the first 48 hours after entrance. Only 4 patients died in this group of 66, thus giving a mortality of 6 per cent in stark contrast to the mortality of the previous series.

Even though these figures cover a period in which there was a changing attitude regarding operation early in the presence of acute osteomyelitis, and even though they indicate that the mortality rate fell when fewer operations on the bone were performed in such cases, they do not prove conclusively that operation early in osteomyelitis is deleterious. Operation may not have been the only factor in the improved mortality. Even those of us who are convinced, upon present evidence, that operation is harmful early in the disease are justified to the extent only of keeping an open mind. The improvement in mortality certainly is not due to more operations or to earlier operation. It may be due largely to factors other than operation. The correct answer to the question whether or not operation is of benefit early for acute hematogenous osteomyelitis may change the mortality rate as little as 1 or 2 per cent in a series of one hundred cases, for the reason that much improvement has followed the use of more recent therapeutic measures. During recent years, particularly in the treatment of other surgical conditions, the profession has had an impressive lesson on the dangers of dehydration and changes in the blood chemistry in sick surgical patients, with the result that whether emphasized in case reports or not, patients undoubtedly now receive more careful attention as to maintenance of normal fluid and electrolytic balance. Moreover, in recent years the repeated re-emphasis of the necessity of maintaining protein requirements has led to the more frequent administration of transfusions. Immunological benefits have resulted from these transfusions. The basic physiology of the patient is thus kept more nearly normal so that his intrinsic defenses against infection are thereby supported. Moreover, extrinsic factors, such as chemotherapy and antitoxin, have been proved of unquestioned value in the management of the condition; and, though it seems a simple procedure and its effect almost incredible, absolute immobilization of the affected extremity appears to be remarkably beneficial.

Such acknowledged therapeutic advances must be taken into consideration in evaluating the results of operation in any stage of the disease. The real status of operation—its relative worth in combatting the disease and its comparative value in relation to other measures—is at present, to say the least, controversial. For that reason all suggestive real proof is desirable. Studies should be made of small and of large series of cases not only in relation to the status of operation but also in reference to details in clinical and experimental investigation relating to each therapeutic measure. Chemotherapy and antitoxin likely may prove the most remarkable advances in the management of the disease. Pure controversy will carry little weight in ultimate, well founded conclusions. Arguments based on the long accepted concept of the pathogenesis—that the disease begins in the end arteries of the metaphysis; that pus under pressure comes to the surface through haversian canals and raises the periosteum for variable distances causing sequestration of the underlying bone—may be worthless, for that concept may be wrong. Thrombosis of the nutrient artery may be the most important change in the local pathological process responsible for determining the extent of sequestration. Many points about the disease remain unanswered; it is not common and intensive studies must be made to prove the value of operation and the best methods of management. One point seems well assured and that is that operation alone early in the disease is not the powerful live saving measure that surgical texts and the teachings of 20 years ago indicated. Other measures now

seem as important, or more important, than surgery. The value of operation on the bone early in the disease still remains an unsettled question. HOWARD MAHORNER.

ACUTE CHOLECYSTITIS WITH PERFORATION

HOW frequently is perforation a complication of the acutely inflamed gall bladder? This question is not readily answered if one includes all of those cases in which slightly bile stained fluid, or secondary abscesses are added to a lesser number in which, due to perforation, a diffuse biliary peritonitis is observed.

Acute cholecystitis manifests itself in two distinct clinical types: First, the usually observed progressive condition which requires several days to reach its peak of severity, both as to symptoms and extent of pathology, but which responds to conservative treatment and can be safely carried over the "waiting" period; second, the fulminating type, the symptoms of which are of short duration, very severe, and in which gangrene and perforation are early complications. In the former group the inflammatory process is rather slow. Peritoneal reaction follows a permeation of the gall-bladder wall by infection or the extension of inflammation; adhesions to the liver, duodenum, colon, stomach, and omentum follow; and secondary abscesses are encountered. Less frequently, due to fixation of the gall bladder to the stomach, duodenum, or colon, fistulas develop, anastomosing the gall bladder to one of these hollow viscera. In either event, this process has occurred rather slowly and therefore the peritoneum has been secured against an escape of bile. During this period the cystic duct quite likely has been occluded by a stone within, or by the inflammatory process, and bile is no longer flowing into the gall bladder so that should perforation occur, there is not an abundance of bile to escape from the gall bladder. However during this time the inflammatory process is likely to spread throughout the biliary ducts and through them or the accompanying lymphatics into the pancreas or liver.

It is in this group of cases that the numerous complications, so much to be feared, are so frequently encountered. It also contributes tremendously to both the morbidity and mortality of gall-bladder disease. Since the progress of the pathology in this group of cases can be measured in days, there is no reason why these patients should not be studied very thoroughly. No factor influencing the element of safety should be overlooked. All of the known laboratory tests which may be used to estimate liver and kidney function and damage should be employed. The degree of jaundice, if any, should be estimated and what effect it has had on bleeding and clotting time known.

These tests can be applied very rapidly. During the period of investigation the patient should receive an abundance of glucose intravenously. No sedatives should be administered and the clinician should make abdominal examinations at frequent intervals.

The fulminating type presents quite a different problem; here as in the first group, history of previously existing gall-bladder disease can be obtained in a majority of the cases, but the onset of the present attack is very sudden. Pain in the upper right abdomen is extremely violent, vomiting is frequently severe, muscle rigidity in the upper right quadrant is pronounced and exquisite peritoneal tenderness is indicated by the slightest pressure on the abdominal wall. The patient usually has some elevation of temperature and the blood count is variously affected. Under the influence of intravenous

fluids the patient's general condition appears improved, but abdominal examinations reveal the same exquisite peritoneal sensitiveness as when first observed or possibly it has spread and increased. This clinical condition suggests a perforating or perforated gall bladder. It has been observed in 10.82 per cent of cases of acute cholecystitis.

The mortality in this group of cases is dependent almost entirely upon the length of time existing after perforation and before operation. It is 16.66 per cent. This may be reduced by earlier operation.

A survey of most of the literature of the past ten years on acute cholecystitis indicates the trend of surgeons of today toward earlier operations for this condition.

The mortality in acute appendicitis was gradually lowered, largely by earlier operation, and the mortality and morbidity of perforated gastric and duodenal ulcers have been greatly reduced by similar efforts.

Likewise, in considering acute cholecystitis, surgeons in general would do well if they realized that early operation will do more to reduce both the morbidity and the mortality in this disease than any other treatment, and that while laboratory tests are of inestimable value, they must not supplant careful clinical observations, for by this latter test must the diagnosis of peritoneal soiling or threatened soiling be made. It is impossible to differentiate a threatened perforation from one that has recently occurred, except by laparotomy.

A biliary peritonitis is known to be highly toxic and fatal in a short time unless adequately interrupted very soon after it has developed.

These facts support the contention that acute cholecystitis with perforation constitutes an abdominal emergency requiring immediate laparotomy, and that the complications of the less rapidly developing cases are of such magnitude that the prevention of them by early operation demands very serious consideration. CHARLES R. EDWARDS.